The Journal of Allergy

VOL. 14 MARCH, 1943 NO. 3

Original Articles

ANTIBODIES TO HISTAMINE INDUCED IN HUMAN BEINGS BY HISTAMINE CONJUGATES

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DALE and Laidlaw,[1] in 1910, demonstrated that the shock produced by histamine was similar to that which occurs in anaphylaxis. Lewis and his co-workers[2, 3] demonstrated the production of a wheal indistinguishable from an allergic wheal by the intradermal injection of histamine. These observations have stimulated many attempts to determine what part histamine plays in the allergic response. That this substance does play a role in at least some phases of these reactions has been demonstrated by Dragstedt,[4] Alexander,[5] Farmer,[6] and others, but its relative importance has not yet been defined.

The exact role of histamine in these reactions could be determined if a substance capable of neutralizing it could be produced experimentally. If the presence of such a histamine-neutralizing substance would inhibit the symptoms of the anaphylactic or the allergic response, there could be no doubt of the importance of histamine in these reactions. Conversely, if no inhibition of symptoms resulted, histamine could be regarded as playing only a minor role in the reaction.

In 1918, Landsteiner[7] showed that when simple chemicals are diazotized and coupled with a protein, an antigen is formed. The specificity of the resulting antigenic complex is determined by the hapten portion. Histamine is a small molecular, rapidly dializable substance which in itself is nonantigenic. To make it antigenic it would be necessary to conjugate it with some substance possessing antigenic properties. In 1940 Fell[8] reported the successful preparation of histamine azoprotein and the results of some immunologic studies made with that compound. Fell's studies, which were carried out in rabbits, demonstrated that a precipitin is induced by histamine azo horse protein which is specific for the histamine (hapten) end of the compound. In view of these very interesting results and because of the controversial nature of the subject, it seemed important to investigate the human antibody response to this histamine conjugate.

Read at the Annual Meeting of the American Association for the Study of Allergy, Atlantic City, June 8, 1942.

TABLE 1

PRECIPITIN STUDIES

CANNON TECHNIQUE (SERUM DILUTION)

	SERUM B								
Dilution of serum	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	CON.
Amount of serum	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0
Amount of antigen particles	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Amount of saline	0	0	0	0	0	0	0	0	0.5
Result	+	++++	++++	++++	++++	++++	++++	0	±

Normal serum controls using same dilutions—all negative.

TABLE II

PRECIPITIN STUDIES

GOODNER TECHNIQUE (ANTIGEN DILUTION)

	SERUM B										
Antigen dilution	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:2560	A C	S C
Amount of antigen	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0
Amount of saline	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.8
Amount of serum	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0	0.1
Amount of particles	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Results	0	+	±	++	++++	++++	++++	++++	0	0	0

TABLE III

PRECIPITIN STUDIES

SERUM	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:2560	SC	AC
W	++	++++	++++	++++	++++	+++	+++	0	0	0	0
WH	0	0	0	0	0	0	0	0	0	0	0
BA	0	0	±	+	++	++++	++++	0	0	0	0
S	0	-	+++	+ ++	++++	+	0	0	0	0	0
K	+	+±	+++	++++	++++	++++	+++	0	0	0	0
B	0	+	±	++	++++	++++	++++	++++	0	0	0
R	++	++	++++	++++	+++	0	0	0	0	0	0

TABLE IV

CHART SHOWING RESULTS OF PRECIPITIN TESTS WITH HISTAMINE AZO-HORSE GLOBULIN (ANTIGEN 51) AND WITH HISTAMINE AZOCASEIN

Antigen dilution	1:4	1:8	1:16	1:32	1:64	1:128	SC	AC
Antigen 51	++	++++	++++	++++	+++	+++	0	0
Antigen casein	+	+++	+++	+++	+++	+++	0	0

RESULTS OF TEST WITH ANTIGEN 51 AFTER SERUM HAD BEEN INCUBATED AT 37° C. FOR ONE HOUR WITH HISTAMINE 1:1000

Dilution	1:4	1:8	1:16	1:32	1:64	1:128	SC	AC
Result	0	0	0	0	0	0	0	0

The histamine azoprotein employed in the present studies was prepared by Fell. Histamine is combined with paranitrobenzoylchloride in chloroform and triethylamine. The resulting paranitrobenzoyl histamine is reduced with ferrous sulfate and ammonia to give paraminobenzoyl histamine (which is a substance that can be isolated in crystalline form). This is diazotized and coupled with protein. The resulting complex is precipitated with trichloracetic acid, centrifuged, washed with dilute hydrochloric acid, redissolved in weak alkali, and adjusted to a pH of 7.5.

This protein complex contains no free histamine. Two per cent antigen solutions contain about 0.8 to 1.0 mg. of bound histamine (as free base) per milliliter. The protein to which the histamine is attached is horse serum despeciated according to the methods of Coghill and Fell.[9] The resulting complex has not produced reactions in persons sensitive to horse serum or dander.

A group of patients with chronic urticaria, atopic dermatitis, contact dermatitis, and vasomotor rhinitis of unknown etiology were picked as subjects for this investigation. Doses of the histamine azoprotein beginning with 0.05 ml. and increasing to 1.5 ml. were given at three- to seven-day intervals over a period of from three months to one year.

Precipitin studies were carried out with the sera of treated patients by employing both the collodion particle technique first described by Cannon and Marshall[10] and the simplified technique described by Goodner.[11] These workers showed that these techniques are highly specific and sensitive enough to demonstrate the presence of precipitins in sera in which no precipitins were demonstrable by any of the other methods of precipitin determination.

For the iontophoretic studies, which will be described later, a current of 1.0 Ma., a standard sized electrode, and a standard time of five minutes were used.

Precipitin reactions were performed on the sera of several patients before treatment with the histamine azoprotein was begun. In no instance were precipitins noted. After a treatment period varying from three months to one year, the patients were bled and precipitin studies were again carried out and gave the results as shown in Tables I, II, and III.

These results demonstrate the presence in the treated sera of a precipitin to the injected complex. Consideration of the complex shows that there are three different portions against which the antibody could be directed: (1) the horse globulin, (2) the azo linkage, and (3) the histamine portion. To determine at which of these three points the precipitins were combining, it was necessary first to test these sera for precipitins against the same histamine complex diazotized onto another protein. Casein was chosen as one far removed from any relationship to horse protein. These studies resulted again in positive precipitin reactions with the treated sera (Table IV). This indicated that there was

combination of antibody with either the histamine complex or the azo linkage and ruled out the horse serum as the specific factor.

To test whether the histamine and not the azo linkage was the factor of importance, the determination of the inhibiting effect of histamine upon the precipitin reaction was the next step to be undertaken. This was done by incubating histamine with a precipitin-containing serum before adding the antigen complex. This procedure resulted in complete inhibition of any precipitin reaction, indicating that the precipitin was specific for the histamine molecule. The results of such an experiment are shown in Table IV. These experiments demonstrate the presence of precipitins specific for histamine in sera of patients treated with histamine azo horse protein.

TABLE V

IONTOPHORETIC STUDIES ON NORMAL SKIN WITH SERUM OF TREATED PATIENTS

SERUM OF PATIENT	DILUTION PRODUCING WHEAL	
	HISTAMINE AND SERUM	HISTAMINE AND SALINE
W.	160,000	640,000
S.	320,000	640,000
W. H.	64,000	640,000
B.	640,000	640,000

Histamine dilutions deteriorate on standing; it is therefore necessary to establish the reaction threshold in the normal skin for each solution of histamine used.

The following illustrates our attempts to determine whether sera containing histamine antibodies would neutralize histamine. Iontophoretic methods employing the techniques described previously were used to determine this point. Mixtures of standard amounts of serum with decreasing amounts of histamine were tested on the skin of the palmar surface of the forearm of a normal individual. One of us (M. B. C.) was used as the subject for all of these determinations. The serum-histamine mixtures were used within a period of from ten to fifty minutes (at room temperature) after their preparation. Controls were run on parallel sites at the same time with the same concentrations of histamine in saline. Preliminary observations had been made on the test subject which indicated that there was no difference in the threshold of reaction when mixtures of histamine and normal serum or mixtures of histamine and saline were used. We therefore used saline in all of the control tests. The results of these studies are shown in Table V. They demonstrate the fact that when histamine was mixed with treated serum, no skin reactions occurred in three of the four experiments until dilutions of from two to ten times the strength of histamine were used as were necessary to produce whealing in the control sites. With one of the four sera studied, whealing occurred with the same dilution of histamine mixture in both the test and the control sites.

These experiments indicate that the treated sera are capable of neutralizing at least part of the histamine after a short incubation

period (at room temperature). We draw these conclusions from our experience with iontophoretic determinations of the in vivo reaction threshold to histamine in well over 100 persons. Reactions are invariably obtained with histamine dilutions of between 1:750,000 and 1:1,000,000. To check these results, we submitted two of these sera to Dr. Gerhardt Katz of New Orleans. Each of these sera was incubated at 37° C. for twenty hours with 0.2 ml. of 1:200,000 histamine base in distilled water and extracted and assayed on the fresh ilium of a normal female guinea pig with the following results:

Serum B—Inactivated 80 per cent added histamine
Serum W—Inactivated 95.3 per cent added histamine

Since Dr. Katz believes that incubation of histamine solutions for twenty hours may destroy between 75 and 80 per cent of the substance, the result of the test with serum B is considered to be negative, but the test done with serum W definitely demonstrated neutralization of 25 per cent of the added histamine by this serum.

The neutralization of histamine after an incubation period as demonstrated by the above experiments is interesting, but it does not necessarily follow that in vivo neutralization of histamine would occur at a rate sufficiently rapid to prevent reactions on direct testing of histamine-treated patients.

TABLE VI

IONTOPHORETIC STUDIES ON TREATED PATIENTS

TREATED SUBJECT	HISTAMINE DILUTION PRODUCING WHEAL	CONTROL SUBJECT	HISTAMINE DILUTION PRODUCING WHEAL
B.	1:400,000	M. B. C.	1:800,000
R.	1:400,000	M. B. C.	1:800,000
R. O.	1:200,000	M. B. C.	1:800,000
S.	1:400,000	M. B. C.	1:800,000
W.	1:800,000	M. B. C.	1:800,000

To establish this important point of in vivo neutralization, the threshold of reaction to histamine was determined by testing dilutions of standard strengths on the skin of treated patients by the iontophoretic method described earlier. Parallel tests were performed on the skin of an untreated person (M. B. C.). Table VI shows the results of five such observations. The skins of four of the treated patients have definitely increased thresholds for histamine.

These observations demonstrate that in certain patients, treatment with histamine azoprotein induces a very rapid capacity for histamine neutralization. As far as we know, no previous methods of treatment with histamine compounds have been followed by any diminution of the skin test threshold. No attempt has been made to report clinical results following treatment with histamine azoprotein.

If greater multiples of neutralization than have been demonstrated to date can be obtained we may be able better to answer the question, Is his-

tamine the toxic substance responsible for allergic reactions? Further experimentation is being carried out along these lines.

SUMMARY

The experiments herein reported have demonstrated:

1. Precipitins specific for histamine in sera of patients treated with histamine azo horse protein.

2. In vitro neutralization of histamine by the sera of patient treated with histamine azo horse protein.

3. In vivo neutralization of histamine as determined by iontophoretic skin tests on patients treated with histamine azo horse protein.

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DISCUSSION

DR. OSCAR SWINEFORD, JR., University, Va.—The role of histamine in allergy is a very active topic to all of us. This paper, I think, is one step toward the ultimate evaluation of the role of histamine in allery. It is, however, simply one step.

I do not think there can be any question about the fact that precipitins were produced in these experiments by the injection of the histamine-protein compound.

I think the controls in Tables V and VI are inadequate. I have found no statement which permits us to accept, as significant, such small differences as 1:160,000 vs. 1:640,000 and 1:200,000 vs. 1:800,000. In fact, the controls themselves in the two experiments differ by 1:160,000. If this difference were added to the test values and subtracted from the control values (a legitimate argument), the test and control differences would be very small indeed. No effort was made to prove that the threshold of some normal persons may not be as high as 1:160,000 histamine. The thresholds for the patients, especially W. and S., were not determined before immunization. It is not necessary to enlarge on this phase of the paper. The work should be repeated with adequate controls because important principles are involved.

Let us leave the details of the paper for just a moment because there are a few things about histamine that have not been but which I think should be emphasized.

In the first place, H-substance is released in a wide variety of conditions other than allergy. A few are the clotting of blood, the injection

of potassium chloride or distilled water, anoxemia, muscle contraction, injection of snake venom, tissue destruction, etc. It seems to me that we are drawing a long bow in attempting to assay its role in allergy unless we also take this nonspecific release of H-substance into account.

Another point about histamine which I think is important: In the early experiments with histamine, the initial assays included cholines and histamine and the so-called slow-reacting substance. The technique as now used to establish histamine equivalents gets rid of the cholines but does not get rid of the so-called slow-reacting substance. So we know, in the histamine equivalent experiments, that we are dealing definitely with two things, perhaps more than two. In fact, only about 30 per cent of the histamine equivalent has been recovered as chemically pure histamine dipicrate. In other words, about 70 per cent of histamine-like substance have not been accounted for as histamine. It seems to me that this 70 per cent of unidentified histamine equivalent constitutes a challenge which must be met before we can even begin to clarify the problem of the nature of the irritants which cause the allergic reactions. I repeat that these ingenious experiments take us one step nearer the evolution of the role of histamine in the allergic reaction.

DR. RALPH G. MILLS, Decatur, Ill.—The assumption apparently has been made that this combination of histamine azoprotein is a stable substance. Perhaps it is under ordinary conditions, but a few little facts that have come to my notice make me wonder just a little about it.

You will remember a year or more ago, Sheldon, Fell, Johnston and Howes* reported their work comparable to this. I have been very fortunate in securing a great deal of that material to use on some patients.

Out of several hundred injections of this sort, a number of instances have arisen in which, as one increases the dosage, slight reactions occur comparable to what you get in ordinary histamine reactions: flushing of the face, weakness, and so forth. In these patients the dosage, naturally, was decreased perhaps to half and then gradually increased again.

Just recently, in fact within the last few days, a case occurred in which, by mistake, a mother, who is a nurse, gave to her girl the same dosage which she gave to herself, she having been entrusted with the work of giving this material to the two, both of whom are very markedly allergic.

The dosage given was 0.2 c.c., initial, in the child, and continuation in her case. Within fifteen minutes there was a very marked reaction comparable to a serum reaction. It took several days for the very marked urticaria to disappear.

The question arises immediately as to whether there was a dissociation of the two components by breakage through of the azo bond or whether possibly some other form of release of the histamine took place.

I just want to call to your attention the fact that as these materials are being used in treatment, they may or may not produce accidents of this sort probably no more severe than that. We hope not.

DR. HAROLD A. ABRAMSON, New York, N. Y.—In experiments on the iontophoresis of histamine, the sensitiveness of the method depends upon the skill and the care of the investigator. In a very short time it is very simple to assay on the skin in the presence of saline, that is physiologic saline, using an electrode of 1 sq. cm. and a current density of 1 Ma.,

*J. ALLERGY 13: 18, 1941.

one part in 3,000,000 of histamine; that is, you always get scattered papules and a flare with that concentration in the presence of saline.

In the absence of saline, I think some of the skilled people who worked with me have readily detected one part in 10,000,000.

Now, are the differences which have been presented significant? I tentatively accept them as significant because the controls run on the same individual show that the experimenter has learned the technique of assaying iontophoretically. This method of assay is very precise if conditions are standardized.

The reasons for the precision are as follows: When histamine is injected, one does not know at what level the needle is put into the skin, and you have a lymphatic distribution coming in, and the histamine may be absorbed much too rapidly or much too slowly because of the differences in size of the lymphatics at different levels in the skin.

On the other hand, when the histamine is given by electrophoresis, it goes through the sweat glands and is always distributed with the same current density at the same level.

For that reason I do not think any controls are necessary other than controls on the same patient, because it is not correct to control an experiment on one patient with an experiment on the skin thickness of another patient.

Dr. H. J. Friedman, Cleveland.—We would like to comment on our controls. We did run normals, that is, normal patients were tested with histamine in saline and with histamine in serum, before we tried this. We got the same results in both cases; there was no difference between our findings with the mixtures of histamine in saline and the mixtures of histamine in serum.

We also think it has been quite definitely established that you do get reactions regularly to histamine with dilutions of 1:1,000,000. It is very seldom necessary to use higher strengths than that if the dilutions have been freshly prepared and standardized.

As far as the stability of the histamine azoproteins are concerned, I cannot say. The only thing I can comment on is our experience with them. We have given comparably tremendous doses of late. We have not reported on this because it is not meant to be a clinical report. We have given as high as 5 c.c. in a short time. As a matter of fact, our dosage was 0.1 c.c., 0.5 c.c., 1 c.c., 2 c.c., and 5 c.c. given any number of times, and we have never yet had any reactions. Whether they will come or not, I do not know.

THE ALLERGENIC PROPERTIES OF THE VEGETABLE GUMS

A Case of Asthma Due to Tragacanth

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REPORTS of sensitivity to various commercial gums have appeared increasingly during the past decade, with gum arabic (acacia) and karaya most often found to be the causative agents. The usual mode of entry is by inhalation, but ingestion and surface contact also have accounted for some cases. The symptoms include vasomotor rhinitis, bronchial asthma, urticaria, atopic dermatitis, angioneurotic edema, and gastrointestinal disturbances. In a large majority of cases sensitization occurs through occupational contact with the gums, and clinical symptoms arise only after a considerable period of exposure. In order to show the wide distribution of these allergens and the conditions under which they may be encountered, the reports thus far published will be briefly reviewed.

I. REVIEW OF THE LITERATURE

Acacia (Gum Arabic).—Experimental work with animals by Maytum and Magath[11] (1932) showed acacia to be mildly antigenic. It caused no reactions in rabbits, but varying degrees of anaphylaxis could be induced in about 63 per cent of the guinea pigs tested. Despite these findings, however, and the low nitrogen content of gum arabic, it has been shown to cause severe clinical symptoms in a large number of persons. The above-mentioned authors observed a patient under treatment for elephantiasis of the leg, who, following a Kondoleon operation, received 500 c.c. of a 6 per cent solution of acacia and 500 c.c. of physiologic saline solution intravenously. No untoward symptoms occurred at the time, but seven months later, when the therapeutic injection was repeated following a second operation, the patient developed nasal obstruction, lachrymation, loss of voice, coughing, and a suggestion of laryngeal stridor. These manifestations were mild and easily relieved by epinephrine. The patient had shown no previous signs of allergy, but her family history was positive.

Much more severe reactions to the intravenous injection of acacia were reported by Studdeford[15] (1937). In three patients suffering from post-partum hemorrhage, infusions of acacia glucose solution produced acute constitutional reactions marked by cyanosis, dyspnea, tachycardia, and pulmonary edema. Two of the patients died, and autopsy upon

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Read at the Annual Meeting of the American Association for the Study of Allergy, Atlantic City, June 8-9, 1942.

one disclosed an extensive destructive lesion of the liver. Believing that impurities in the acacia preparations might have caused these untoward effects, the author tried fresh material from another supply house, but this produced similar results in three other patients, one of whom died.

Studdeford observed that recent experimental work has shown the likelihood of liver damage following the intravenous injection of acacia. It seriously disturbs the red blood cells, interfering with the normal gaseous interchange, increasing the tendency to rouleaux formation, and accelerating the sedimentation rate. Conglutination of red cells may occur, producing blockage followed by edema and hemorrhage.

Experiments on dogs by Hall, Gibson, and Weed[7] (1940) showed that repeated intravenous injections of the gum damaged the carbohydrate and serum protein functions of the liver, as evidenced by changes in the glucose and galactose blood sugar tolerance curves and determinations of plasma proteins. However, no effect was observed on the hepatic cells, nor was there any blocking of the reticulo-endothelial system comparable to that produced by some colloidal substances.

Spielman and Baldwin[14] (1933) described a case of acacia sensitivity in a plaster molder employed in a candy factory. He developed vasomotor rhinitis and bronchial asthma after working about six months in the plant. Direct tests produced a marked reaction to the factory dust containing crude acacia and also to purified acacia. Passive transfer tests likewise were positive.

Allergy to acacia among printers appears to be growing more and more frequent. The gum is used in solution with dextrin, alcohol, and water as a drying, or offset, spray for printed material. The spray fills the workrooms with a fine mist which the employees unavoidably inhale unless protected by a mask.

Feinberg and Schoenkerman[5] (1940) reported a case of bronchial asthma in a printer which they attributed to this cause. The patient gave positive skin reactions to gum arabic and also to karaya. Following this, Bohner, Sheldon, and Trenis[1] (1941) published ten similar cases. All their patients reacted to gum arabic by direct tests, and passive transfer was positive whenever tried. These printers had been exposed to the acacia solution for periods of from two weeks to a year. The authors state that "the direct transfer tests were negative to Indian gum and tragacanth" ("Indian gum" probably referring to karaya).

King[9] (1941) treated one case of bronchial asthma and another of vasomotor rhinitis in printers, both of whom were positive to acacia. These patients were of allergic constitution and reacted to other substances, such as orris root, egg white, house dust, and pollen, but clinical symptoms did not appear until they became sensitized by gum arabic in their occupation. Attempts at desensitization in one patient were unavailing while he remained in his job. King refers to the New

York State Department of Labor Bulletin for 1940,[13] which also mentions a number of cases of rhinitis and asthma among printers, probably due to gum arabic.

According to our search through the literature, Levin[10] (1939) appears to have been the first to record a case of sensitization to acacia in the printing trade. It probably is only in recent years that this type of offset spray has been brought into use.

Feinberg and Schoenkerman[5] described the case of a furniture dealer with asthma of many years' standing, which probably was due to infection. Nevertheless, the patient gave a marked skin reaction to acacia, which proved to be an ingredient in some of his furniture preparations. Desensitization with the gum appeared to afford some temporary relief.

Karaya Gum.—Bullen[3] (1934) was the first to report a case of allergy to karaya. His patient developed vasomotor rhinitis from contact with the gum in hair-waving lotion. Since that time such reports have become quite numerous. Feinberg[4] (1935) observed bronchial asthma in a hairdresser from the same cause. Scratch tests with powdered karaya gum, sodium benzoate, tragacanth, acacia, and another brand of hair-waving fluid all were negative except that with karaya, which, he said, produced an "enormous reaction."

Bowen[2] (1939) reported five cases of urticaria due to karaya. One patient had associated respiratory symptoms. He gave details of one case in which the urticaria was accompanied by severe pruritus and some lesions of angioneurotic edema, frequently involving the joints. The edematous lesions were succeeded by patches of hyperpigmentation. This patient's symptoms were traced to karaya gum in Dr. Wernet's dental powder, used for holding her denture in place. She gave no family history of allergy.

Figley[6] (1940) observed sixteen women with allergic symptoms, all of whom gave positive reactions to scratch tests with karaya. The family history was positive in all but two. The allergen was absorbed by ingestion and surface contact as well as by inhalation, and the chief manifestations were perennial rhinitis, asthma, atopic dermatitis, urticaria, and gastrointestinal distress. Wave lotions, laxatives, emulsified mineral oil, gelatins, diabetic foods, tooth pastes, and denture adhesive powders were the sources of sensitization.

In investigating the effect of Mucara, a laxative containing karaya, Ivy[8] found that 7.8 per cent of eighty-nine test subjects who ingested this preparation complained of mild abdominal cramps or other discomfort for which he could not account. Figley suggested the possibility that these patients were slightly sensitive to karaya through having previously ingested it in some food or confection.

Feinberg and Schoenkerman[5] analyzed ten cases of allergy to karaya resulting from contact with hair-waving lotions or powders. Respiratory

symptoms were the chief complaint in nine of the patients, one of whom had an associated dermatitis of the face and scalp. The tenth complained only of dermatitis of the face and neck. Cutaneous reactions to karaya were consistently positive in all the patients by direct test and also by passive transfer when this was performed. On being tested with other gums, in accordance with the authors' established routine, seven patients gave negative reactions, two reacted slightly to tragacanth alone, and one to acacia and tragacanth. The authors believed karaya to be the sole cause of clinical symptoms in four of the patients and a contributory factor in the remainder. In one patient with bronchial asthma, desensitization with karaya produced moderate improvement; in another, a change to tragacanth preparations proved beneficial.

The most common ingredients in hair-waving lotions are acacia, tragacanth, linseed gum, quince seed gum, karaya; boric acid, sodium, potassium, and ammonium carbonate; alcoholic keratin, coloe, petrolatum, cera-flux, glyco wax A, and paraflux. According to Figley, however, karaya has almost supplanted such gums as linseed and quince seed, and this fact may account for the growing number of allergic manifestations reported from contact with these preparations.

Gum Tragacanth.—Reports of sensitivity to tragacanth are extremely rare in the literature. One case has been described by Feinberg and Schoenkerman, in which a hay fever patient suffering from severe urticaria and eczematous dermatitis of the hands gave a marked reaction to tragacanth. The authors believed her cutaneous symptoms to be due to a hand lotion containing this gum but were unable to follow the case closely enough to obtain conclusive proof. We already have mentioned that three of their karaya-sensitive patients gave slight reactions also to tragacanth. They stated that they were unable to find any cases in the literature that incriminated tragacanth as an allergen, but "because of its close relation to karaya gum," they employed it in routine testing.

Owing to its comparative rarity, therefore, the following history* may be of particular interest. We believe it to be the first thoroughly authenticated case of clinical allergy caused by sensitivity to tragacanth.

B. T., white, female, aged 26 years, came to Gouverneur Hospital on July 7, 1941, to ask for desensitization to certain commercial gums which she believed to have caused her respiratory symptoms. She gave the following history:

In December, 1939, she went to work in the office of a New York gum factory. This firm imports various commercial gums from the Orient and mills them on the upper floor of its office building. The material is passed from one floor to another through a chute which is not airtight,

*This case report was presented before the Associated Allergy Clinics of Greater New York at their fall meeting, Nov. 6, 1941. The presentation was made by Dr. Maury D. Sanger and discussed by the author.

and office workers as well as the millers are exposed to dust given off by the gums. The patient's desk was situated close to the chute, samples of the material were handled by her, and other samples were exposed in open containers on the office floor. Moreover, she frequently came in contact with the mill workers.

When the patient began to work in this place she was in perfect health and remained so for about a year. Then, in December, 1940, she became troubled with what she supposed to be a persistent head cold, with blocking of the nose, frequent sneezing, and profuse nasal discharge. She began to feel "run down" and decided to remain at home to recuperate. On a brief visit to the factory on New Year's Day, 1941, however, she apparently contracted a "fresh cold." After her return to work this also persisted, and by the end of February, fourteen months after her first contact with the gums, she began to cough and wheeze.

On March 3, 1941, fifteen months after first exposure, and coincident with the milling of an unusual amount of tragacanth, the patient was seized with a severe attack of asthma, lasting for eight hours, and finally was relieved by epinephrine.

From that time on, up to June 20, 1941, similar attacks occurred whenever she returned to her job after sick leave or vacations. All were relieved by epinephrine. After an extremely severe seizure on June 20, she resolved never to return to the factory. But, in order to prove that the gums were responsible for her trouble, she tried various temporary positions in other kinds of business. In the new surroundings, no untoward symptoms occurred.

Convinced now that she was allergic to the gums, and her return to the job being greatly desired, the patient came to our clinic to be desensitized.

Personal and family history, as given, were completely negative. Physical examination revealed no sign of infection in the nasopharynx or sinuses. X-ray examinations of the chest and sinuses also were negative.

Direct skin tests with the usual allergens produced no response, but when gum tragacanth, 100 units, was tried, a marked reaction occurred. Gum arabic, 1,000 units, also produced a strong reaction. Passive transfer tests with these two gums were strongly positive down to the 1:100 serum dilution. On the other hand, direct tests with karaya up to 5,000 units failed to provoke any response.

Immunization treatment with tragacanth was attempted with great caution for fear of untoward reactions, and the dosage increased at first only from 5 to 10 units for each successive treatment.

After receiving thirty injections, the patient believed herself to be immunized and decided to revisit the gum plant. Upon only a half-hour exposure, however, she experienced an ominous tightness in the chest.

TABLE I

OCCUPATIONAL ALLERGY IN A GUM FACTORY

CASE NO.	NAME	SEX	AGE (YR.)	TYPE OF WORK	TIME EMPLOYED	ALLERGIC SYMPTOMS	REACTION TO TESTS			REMARKS
							KARAYA	GUM ARABIC	TRAGACANTH	
					Office Workers					
1	M. W.	M	63	Manager	30 yr.	None	Neg.	Neg.	Neg.	--
2	V. L.	M	25	Chemist	4 yr.	None	Neg.	Neg.	Neg.	--
3	M. K.	F		Clerk	1 yr.	Rhinitis, asthma	--	Mkd.	--	Left job
4	B. T.	F	27	Secretary	1 yr.	Rhinitis, asthma	Neg.	Mkd.	Mkd.	Left job
					Factory Workers					
5	M. B.	M	42	Packer	11 yr.	Nasal clogging, dyspnea	Neg.	Mod.-Mkd.	Neg.	--
6	G. S.	M	35	Miller	2½ mo.	Bronchial asthma	Neg.	Neg.	Neg.	Asthma due to infection
7	L. O.	M	33	Miller	12 yr.	None	Neg.	Mod.-Mkd.	Neg.	--
8	J. P.	M	21	Elevator operator	1½ mo.	None	Neg.	Neg.	Neg.	--
9	J. C.	M	39	Laborer	15 yr.	None	Neg.	Neg.	Neg.	--
10	E. W.	M	38	Shipping clerk	4 yr.	None	Mod.	Mod.-Mkd.	Neg.	--
11	A. O.	M		Foreman	5 yr.	Nasal clogging, sneezing	Neg.	Mod.-Mkd.	Mod.	--
12	J. S.	M	22	Miller	1½ yr.	Sneezing, dyspnea	Mod.	Mod.-Mkd.	Mkd.	--

Summary

	NUMBER EXAMINED	NUMBER AFFECTED	NUMBER NOT AFFECTED	CAUSE OF SYMPTOMS		POSITIVE SKIN REACTIONS		
				GUMS	INFECTION	KARAYA	GUM ARABIC	TRAGACANTH
Total	12	6	6	5	1	2	7	3
Office workers	4	2	2	2	0	0	2	1
Factory workers	8	4	4	3	1	2	5	2

On reaching home she was seized with an exceedingly severe attack of bronchial asthma. A number of injections of epinephrine were required before the paroxysms subsided, and she remained ill for a week. This experience caused the patient to abandon all hope of returning to her job, and she also discontinued treatment.

II. SENSITIZATION TO GUMS AS AN OCCUPATIONAL RISK

The striking character of the foregoing case and the excellent field for research provided by a factory solely concerned with the handling and processing of allergenic gums led us to study the incidence of sensitivity among the other employees.

We found that the firm had been in business for more than a century, and during that time certain employees in the mill (formerly in a separate building) had had symptoms of vasomotor rhinitis and severe bronchial asthma after contact with tragacanth, gum arabic, and karaya. In most cases, the affected workers had to leave their occupation, but some were able to carry on, and, in time, appear to have become, so to speak, immune.

In recent years the milling has been done in the same building with the executive offices, and we learned that another female office worker, previous to our survey, had been obliged to give up her work on account of nasal symptoms and bronchial asthma, coming on about a year after first exposure. Her physician had found her to be sensitive to gum arabic.

In order to gain more information as to the sensitizing properties of the gums and their antigenic relationships, we carried out a study among both the office and mill workers. We were unable to examine the entire personnel, but those who were willing to undergo tests made up a good cross-section.

No further complaints were discovered among the office force, but investigation of the millers revealed a somewhat different picture. Most of the men had been in the mill for a number of years under conditions of massive exposure, and the factor of mechanical irritation as well as prolonged contact was involved. Nevertheless, many of them had escaped untoward symptoms. Table I shows the results of our examinations thus far.

It will be noted that 50 per cent of all the workers examined had respiratory symptoms of an allergic nature. Among the four office employees, one* was sensitive to gum arabic and another to gum arabic and tragacanth but not to karaya. These workers had to leave their jobs. Of the eight mill workers, three had nasal clogging and sneezing (with or without constriction of the chest) when in contact with certain gums, and these three were found sensitive to the materials by direct

*This refers to M. K., who had left the plant previous to our survey. However, since we were able to obtain her history, it has been included.

skin tests. One had asthma traceable to infection in the sinuses and unrelated to his occupational contacts.

Comment.—In view of the contradictory findings in a few of these cases, the question arises—how many of the men who gave positive skin tests, but denied having symptoms, were concealing their complaints for fear of endangering their jobs? With one or two of them we had a strong impression that this was the case. Nevertheless, the fact remains that a certain number of employees definitely remained free from untoward symptoms and had no signs of clinical pathology discoverable by physical or roentgen examination or by skin tests. Those who did acknowledge allergic symptoms, with one exception, also gave positive skin reactions to one or more of the gums. Hence, it is clear that irritation and prolonged contact with tragacanth, gum arabic, and karaya affect some persons but fail to affect others working under the same conditions. We must conclude that the individuals who become sensitized have an inherent predisposition to allergy, which probably is hereditary, although no family history of hypersensitiveness could be elicited in any of these cases.

The case of B. T. is the most clear-cut of any that came under our observation and the most enlightening. First, it demonstrated the fact that gum tragacanth as well as gum arabic is a sensitizing agent capable of producing severe respiratory symptoms in predisposed individuals. Second, the patient was found, by both direct and passive transfer tests, to be sensitive to gum arabic and tragacanth but not to karaya, despite the fact that the antigenicity of karaya has been so well established. This tends to disprove the general assumption that all these gums are closely related. Third, it was shown that a period of time was required after first contact to bring forth the acute sensitivity. Fourth, since the treatments though limited were supplemented by long absence from exposure and yet failed to confer any degree of immunity, desensitization probably would be unavailing.

III. ANTIGENIC RELATIONSHIP OF THE GUMS

The general impression has been that the three gums under consideration are closely related both antigenically and botanically, but few observers appear to have carried out in vitro and in vivo neutralization experiments with the sera of patients known to be clinically sensitive to them. Since our clinical findings in the cases of B. T. and A. O. seemed to disprove the theory of a common antigen in karaya and the other two gums, we decided to make such studies in order to determine the antigenic relationship of tragacanth and gum arabic.

Sera were obtained from all the workers found to be sensitive, and all except one gave a positive passive transfer. For the neutralization studies, however, only one serum, that of B. T., remained suitable for study. A few hemolyzed, and the patients refused to give more blood. In one case the Wassermann was doubtful.

Following is the result of our studies with B. T. serum:

Exhaustion-Site Studies (Figs. 1 and 2).—

Method: Duplicate sites in nonatopic recipients were passively sensitized by injecting 0.1 c.c. of B. T. serum, which was clinically sensitive to gum tragacanth and gum arabic. The next day, when the reagins were fixed in the tissues, the first site (above) was tested with

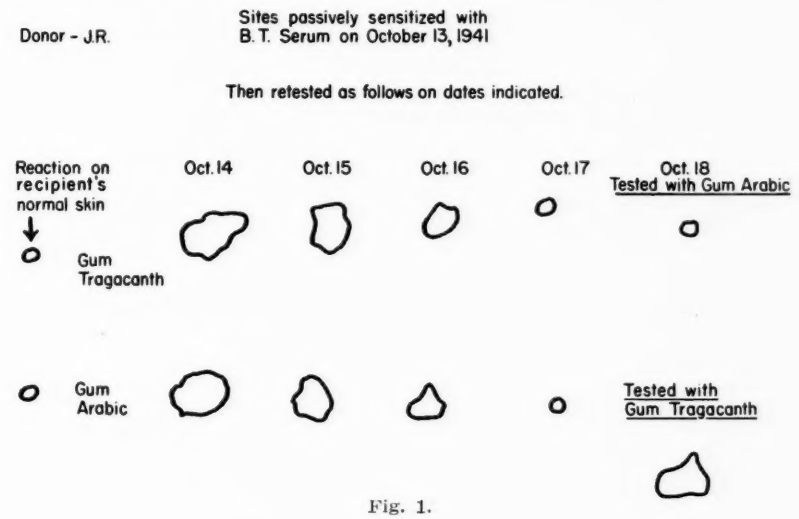

Fig. 1.

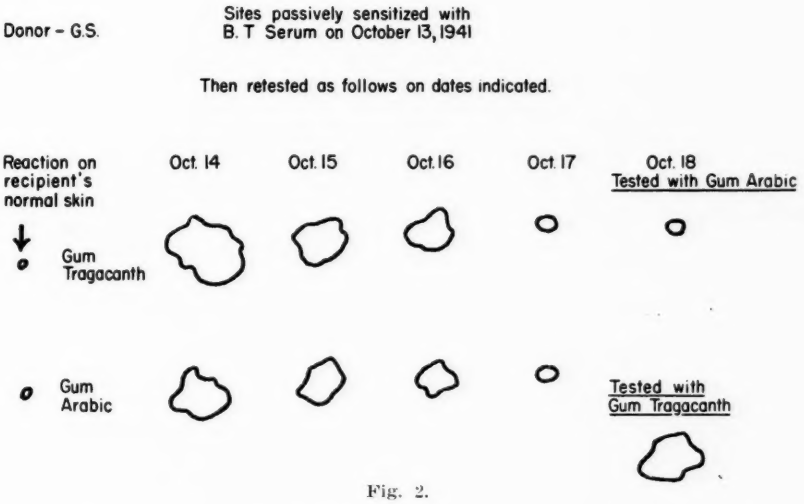

Fig. 2.

gum tragacanth and then retested daily until no reaction occurred. The following day the site was tested with gum arabic. The second site was desensitized in the same way to gum arabic and then tested with tragacanth.

Results: In both donors the reagins to gum arabic were completely neutralized by tragacanth, but gum arabic failed to neutralize the reagins to tragacanth.

In Vitro Neutralization Studies (Figs. 3 and 4).—

Method: Having previously determined that the immediate and forty-eight-hour tests showed neutralization at 500 to 700 units,* we prepared in the test tube under sterile precautions a mixture of two parts extract (0.2 c.c. of 5,000 units, representing 1,000 units) to one

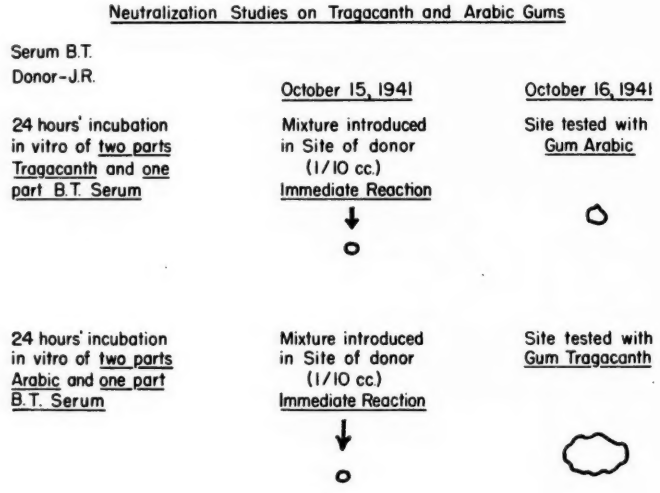
Neutralization Studies on Tragacanth and Arabic Gums
Serum B.T.
Donor-J.R.
October 15, 1941
October 16, 1941
24 hours' incubation in vitro of two parts Tragacanth and one part B.T. Serum
Mixture introduced in Site of donor (1/10 cc.)
Immediate Reaction
Site tested with Gum Arabic
24 hours' incubation in vitro of two parts Arabic and one part B.T. Serum
Mixture introduced in Site of donor (1/10 cc.)
Immediate Reaction
Site tested with Gum Tragacanth

Fig. 3.

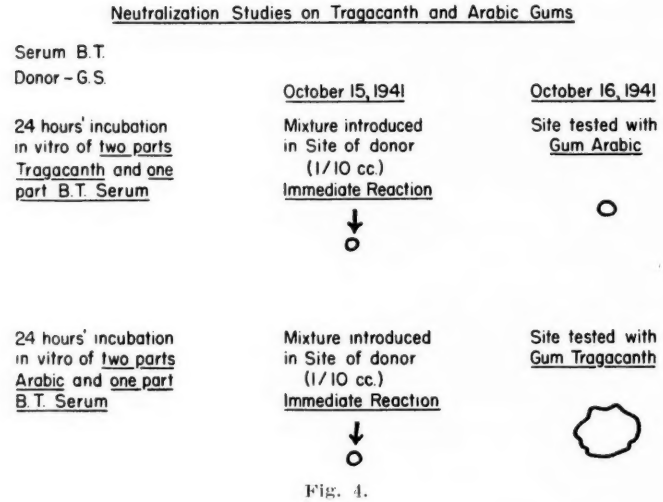
Neutralization Studies on Tragacanth and Arabic Gums
Serum B.T.
Donor - G.S.
October 15, 1941
October 16, 1941
24 hours' incubation in vitro of two parts Tragacanth and one part B.T. Serum
Mixture introduced in Site of donor (1/10 cc.)
Immediate Reaction
Site tested with Gum Arabic
24 hours' incubation in vitro of two parts Arabic and one part B.T. Serum
Mixture introduced in Site of donor (1/10 cc.)
Immediate Reaction
Site tested with Gum Tragacanth

Fig. 4.

part serum (0.1 c.c.) for each gum, tragacanth and arabic. After being allowed to stand in the icebox for twenty-four hours, each mixture was injected in 0.1 c.c. amounts into duplicate sites on nonatopic subjects.

*This was done by mixing in the test tube increasing amounts of antigen with a fixed amount of sensitive serum, allowing it to incubate in the icebox, and then injecting test amounts into a nonatopic donor. The immediate reaction was observed, and forty-eight hours later each site was tested with 1,000 units of the gum antigen, and the neutralization point was noted.

Twenty-four hours later the sites injected with serum neutralized to tragacanth were tested with gum arabic, and vice versa. Duplicate control sites, having been prepared with two parts physiologic saline solution and one part serum, also were tested with each gum.

Results: Here, too, we found that tragacanth neutralized the reagins to itself as well as to gum arabic, but arabic, while neutralizing its own reagins, failed to neutralize the reagins to tragacanth.

Comment.—The direct skin tests in the case of B. T. suggested a probable antigenic relationship between tragacanth and arabic, but none between either of these gums and karaya. The serologic studies both in vivo and in vitro confirmed the relationship between the two gums to which the patient was clinically sensitive, since it was shown that gum tragacanth completely neutralized the reagins to gum arabic, but that gum arabic failed to neutralize all the reagins to tragacanth. It was noted that tragacanth and arabic extracts were similar in nitrogen content but that direct skin tests on this patient elicited a greater reaction to tragacanth. The impression was thus gained that tragacanth extract either contains an antigen not present in gum arabic or that it is richer than gum arabic in atopic excitant content.

IV. NATURE AND DERIVATION OF ALLERGENIC GUMS

This is a subject on which the information from various authoritative sources long has been indefinite and conflicting. Medical knowledge is therefore in a state of confusion, and it is small wonder that statements appearing in the literature show many contradictions.

We have consulted different authorities and have obtained the following information from the United States Dispensatory for 1937:

The term gum, often loosely applied to the resinous exudate of plants, refers more correctly to exudates which contain a carbohydrate that is capable of forming with water mucilaginous mixtures. The belief that gums differ from resins in being soluble in water and insoluble in alcohol is incorrect. Some gums do not actually dissolve in water but simply swell into viscid mixtures with it, and some gums are soluble in alcohol.

The gums that are most often considered identical, or whose names are frequently confused with one another, are described as follows:

Bassora Gum (Caramania Gum, or Hog Gum): Bassora gum is a collective term for a group of high-colored gums somewhat resembling tragacanth. The soluble part is arabin and is said to constitute about 11.2 per cent. The insoluble part consists of bassorin, with a small proportion of saline substances. The gum is used as an adulterant for acacia and can be distinguished by its insolubility in water. Its botanical origin is doubtful.

Karaya Gum: Karaya gum is known as Sterculia gum or Indian tragacanth. It is derived from *Sterculia urens* Roxb. (Fam. Sterculiaceae), of Asia, and possibly other species of Sterculia. It is found in irregularly shaped, pinkish brown or light

brown pieces and has an acateous odor. When boiled with 5 per cent potassium hydroxide solution, it shows only a slight tinge of brown, whereas tragacanth thus boiled becomes a bright yellow and gives a stringy precipitate. Tragacanth is more mucilaginous than karaya, and karaya has greater acidity (due to acetic acid) and dissolves more readily in cold water. Nevertheless, powdered karaya often is used as a substitute for powdered tragacanth and loosely *called* tragacanth.

India Gum (Ghatti Gum): The term India gum has been applied to many different substances, including Bassora gum, Sterculia gum, and Ghatti gum (Gummi indicum). The British Pharmacopoeia in 1914 recognized Ghatti gum as India gum. It is derived from different species of the Indian tree *Anogeissus latifolia* (Fam. Combretaceae). It is used in pharmacy for the same purposes as acacia. Its mucilage is more viscid but less adhesive than acacia and is usually employed in connection with tumeric, with which there is some specific combination.

Gum Arabic (Acacia): Gum arabic comes from the stems and branches of *Acacia senegal* Willdenow (Fam. Leguminosae), or some other African species of Acacia. It is whitish yellow or light amber in color and is insoluble in alcohol but almost completely soluble in water, the solution being acid. It is composed essentially of the calcium salt of arabin, or arabic acid. The gum is an effective demulcent and is extensively used in drugs, pills, and lozenges.

Gum arabic often is adulterated with Mesquite gum, from a Mexican plant, *Prosopsis juliflora* (Fam. Leguminosae).

Tragacanth Gum: This substance is an exudation from *Astragalus gummifer* Labillardière (Fam. Leguminosae) and other Asiatic species of Astragalus. In the past there has been much doubt as to its botanical source, but it now is known to be of the above genus and family. It is entirely insoluble in alcohol and seems to be composed of two different constituents, one being soluble in water and resembling gum arabic, and the other swelling in water but not dissolving. The soluble part, which is much the greater, is said by A. G. Norman (1931) to consist of uronic acid and arabinose in about equal proportion, which compose 94 per cent, plus small amounts of cellulose, starch, and protein substances. The insoluble part is mostly bassorin.

Tragacanth is sometimes adulterated with Sterculia (karaya) and Ghatti gum but more frequently with acacia. The difference between true tragacanth and Sterculia can be proved by a distillation test with water and determination of the acidity, which is greater in Sterculia.

According to Chemical Abstracts (1939), tragacanth contains enough starch to give a blue color with iodine solution, but acacia contains no starch. The methoxyl (CH_3O—) indexes of the three gums under consideration are: acacia, 0-12.4; tragacanth, 18.6-38; karaya (Sterculia), 0.

Figley[6] quotes Norman (1929) to the effect that no essential difference exists between gums and hemicellulose; in both, hexose and pentose are linked with uronic acid. He also quotes Solis-Cohen, who states that arabin, bassorin, and cerasin are the proximate principles of gums, and that gums are chiefly pentosans.

Bohner, Sheldon, and Trenis[1] say that acacia is classed chemically as an inert colloid and is considered to be a polysaccharide member of the carbohydrate family, related polysaccharides being glycogen, dextrin, and starch. All of these are amorphous, odorless, and translucent, and on hydrolysis yield one or more sugars, usually pentoses and hexoses.

In discussing Bullen's paper,[3] Baldwin said the fact that gums are listed as polysaccharides is misleading, because in the case of acacia, 0.5 per cent of total nitrogen is present and it also gives a positive biuret test. In an analysis of three samples purchased in the open market, Bohner and his associates found an average of 0.48 per cent of nitrogen and a positive biuret test. They note that Uhlenhuth and Remy[16] found 0.3 per cent of nitrogen in samples of purified acacia.

Figley[6] stated that the nitrogen content of karaya is only 0.1 per cent.

V. SOURCES OF CONTACT WITH ALLERGENIC GUMS

We have compiled the following list from data gathered by many of the authors quoted in this paper and from other available sources. Since we know that the various gums frequently are substituted for one another and adulterated by one another and by other gums, no attempt at separate classifications has been made:

Adhesive pastes
Artificial flowers
Body and drier in lithograph inks
Candy (e.g., gumdrops and jellies)
Cement
Cheese
Cigar manufacture
Coating for special thread
Custards (e.g., in factory-made pasteries, etc.)
Denture adhesive powders (Dr. Wernet's, Dent-A-Firm, Stix)
Diabetic foods (e.g., soy bean and almond wafers)
Emulsions (e.g., mineral oil, cod-liver oil, turpentine, almond, and flavor emulsions)
Fireworks
Furniture polishes
Gelatines
Glues
Ice cream mixes
Insecticides
Laxatives (e.g., Imbicoll, Mucara, Squibb's Petroleum and Agar)
Linoleum and oil cloth
Lotions (cosmetic, for hand care, hair-waving, etc.)
Luster for textiles
Match manufacturing
Metal polish manufacturing
Mucilages
Paints
Pills
Porcelain and pottery manufacture
Printing ink manufacture
Process engraving
Salad dressings (factory made)
Shoe polishes
Sizing of paper and textiles
Sprays (offset in printing trade)

Starch (special)
Suppositories
Toothpastes (Listerine and Lactora)
Textile printing
Vaginal jellies
Varnishes
Water colors (transparent)

No doubt these gums also occur in many other preparations in which their presence has not yet been disclosed, and the sources of contact probably are even more widespread than the above list would indicate.

SUMMARY

1. The published reports of sensitivity to vegetable gums have been reviewed. These reveal that the chief sources of sensitization are karaya gum in hair-waving lotions and acacia in the offset sprays used in the printing trade. Although the allergens may enter the system by ingestion, injection, or surface contact, inhalation is the most common route, and respiratory symptoms predominate.

2. The first well-established case of sensitization to tragacanth is reported. This case led to a study of the incidence of gum sensitivity among the workers in a gum factory, which has brought forth the following facts: (a) that gum sensitization is an occupational risk for predisposed persons; (b) that a period of time (usually about a year) is required after first exposure for the development of acute symptoms; (c) that tragacanth is a powerful allergen capable of causing extremely severe reactions; (d) that desensitization with allergenic gums is difficult, if not impossible; (e) that some workers who become sensitized may afterward spontaneously develop tolerance.

3. The antigenic relationship between gum arabic and tragacanth has been studied by means of in vivo and in vitro experiments with sensitive sera. It was found that tragacanth is able to neutralize all the reagins to gum arabic but that arabic only partially neutralizes the reagins to tragacanth. Thus it appears that, while an antigenic relationship probably exists between these gums, and although the nitrogen content may be the same in both extracts, tragacanth must either contain an antigen not present in arabic or its extract must be richer in excitant content. The relationship between karaya and the other gums was not studied.

4. Consultation of various authorities on the botanical origin of the three gums revealed that gum arabic (*Acacia senegal*) and tragacanth (*Astragalus gummifer*), although differing in genus and species, are members of the same family (Leguminosae). Karaya, on the other hand, belongs to an entirely different family (Sterculiaceae). This fact may have some bearing on the antigenic relationship of the gums as brought out in our studies.

5. The known sources of possible contact with allergenic gums have been listed.

6. In conclusion, a review of the entire subject of gum sensitization shows it to be an increasing risk for predisposed individuals, especially through occupational contact, as demonstrated in hairdressers, confectioners, printers, employees of gum plants, and other workers who are subject to prolonged exposure.

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235 EAST 22ND STREET

DISCUSSION

DR. KARL D. FIGLEY, Toledo, O.—It may be of interest to know that since I read Dr. Gelfand's paper I reviewed twenty-six cases of karaya gum sensitivity. These were all women who contacted karaya gum chiefly by inhalation of wave-set material containing the gum. Two of these persons were beauty parlor operators and the remainder were housewives or unmarried women. These twenty-six persons were all tested with acacia and tragacanth. None of them reacted to tragacanth; four, while giving negative scratch tests to acacia, did give 1 or 2 plus to acacia on intradermal testing. I think the reason none of my patients were definitely sensitized to acacia or tragacanth, is that in all probability they never were exposed to these substances by inhalation. Therefore, they obviously would not be sensitized.

It is interesting that Dr. Gelfand's twelve patients studied were presumably equally exposed by inhalation to the three gums; that the greatest number (six) reacted to gum arabic; that tragacanth was next with three reactors; and karaya last with two reactors. May one assume from this that arabic is the most potent allergen of the three?

Dr. Howard Osgood, Buffalo, N. Y.—I have been testing routinely for some time with five different gums but have done no passive transfer studies. Just before leaving for this meeting, I pulled out at random the records of 100 allergic patients and summarized the results of the tests with these gums. I thought it might be of interest in connection with the present paper.

The gums used were acacia, tragacanth, quince seed, karaya, and ghatti. The latter is sometimes substituted for karaya in what is known as India gum. The concentrated extracts were 1:33 or 1:100 of the dry gum in Coca solution, depending on the ease of Seitz filtration. A 1:10 dilution was made up from the concentrated extract, and tests were carried out in each patient with both strengths.

Of the 100 patients tested, there were only two who failed to give skin reactions in some degree (slight, moderate, or marked) to one or more of the gums, in weak or strong dilution. There were twelve patients who reacted to one gum only, twenty-two who reacted to two only, twenty-two to three gums, fourteen to four, and there were twenty-eight patients who reacted in some degree to all five gums.

To determine the relative skin-exciting properties of the different gums, or conversely the relative skin reactivity of this group of 100 patients to the different gums, I have tabulated the maximum reaction given by each patient to each gum, without indicating to which strength (concentration or 1:10 dilution) the maximum reaction occurred. For example, to acacia thirty-four patients gave only a slight reaction to either dilution, thirty-three gave a moderate reaction, and twelve gave a marked reaction to one or the other dilutions. Ghatti gum gave the most numerous reactions, ninety-three patients reacting to some degree. Karaya gum with only twenty-five patients reacting, gave the fewest.

Table I

Maximum Degree of Skin Reactions to Each Gum

	Number of patients giving				
	Slight only	Moderate only	Marked	Total	Moderate or marked
Acacia	34	33	12	79	45
Ghatti	42	36	15	93	51
Karaya	25	6	5	36	11
Tragacanth	26	12	10	48	22
Quince seed	42	16	4	62	20

I tried to see what cross reactions there might be to these five gums and have tabulated the frequency of associated reactions in single patients. Moderate and marked reactions only were considered. Eighteen gave moderate or marked skin reactions to acacia and ghatti gums and to no others, this being the most frequent association. The number of other patients giving reactions to two gums only showed the following associations: acacia-tragacanth, 2; acacia-quince, 2; ghatti-karaya, 2;

ghatti-quince, 1. The number of patients showing reactions to three gums only gave the following associations: acacia-ghatti-quince, 9; acacia-ghatti-tragacanth, 5; ghatti-tragacanth-quince, 1. Eight patients gave moderate or marked reactions to four or to all five gums. It will be seen that the most frequent association of moderate or marked reactions occurred with acacia, ghatti, and quince seed.

I am presenting this statistical summary for what it may be worth and draw no definite conclusions. I am not ready to state that these positive skin reactions indicate clinical sensitivity to gums, although in a small number of these 100 patients this was definitely the case.

My own feeling is that in the dilutions used, the gum solutions may be intrinsically slightly irritating, thus explaining the numerous slight and moderate reactions. Typical marked reactions occurred in forty-six patients, most frequently to ghatti, acacia, and tragacanth. My second opinion is that there may be common allergens in some of the gums.

I have not delved into botanical relationships, as has Dr. Gelfand, but from his results, and from my meager observations, it would seem that further work with these gums along the lines laid out by Dr. Gelfand would be well worth while.

INSULIN HYPERSENSITIVITY WITH DESENSITIZATION

Report of a Case

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THE use of insulin in the treatment of diabetes is usually accompanied with little discomfort. However, there are patients in whom there are, more or less, reactions to the insulin injected, this reaction being usually of an allergic nature. That insulin may cause allergic reactions, as do other foreign proteins, was recognized from the earliest days of its use.[1] The reaction may be due to hypersensitivity to the insulin factor itself, to hypersensitivity to the pancreatic tissue of the specific animal source, to some extraneous substance of the pancreas not removed in the manufacture of the product, and, since the advent of the newer protamine zinc insulin, to the reactions from these added substances.

Real sensitivity to insulin, per se, regardless of its commercial source, presents a serious problem. The danger to the patient from anaphylaxis may be as real as the danger from the diabetic ketosis.

The analysis of crystalline insulin has shown it to be a protein containing an average of 0.006 to 0.01 mg. of nitrogen per unit,[2] which, according to Vaughan,[3] is sufficient to be of allergenic significance. Lewis[4] demonstrated that insulin is a complete protein capable of producing sensitization. From his work, Lewis[4] concluded that insulin protein was an active antigen and that it is without species specificity, since it has no antigenic activity in common with the other protein derived from the same species which are strongly species specific.

Wasserman and his associates[5] have been able to demonstrate complement-fixing antibodies to insulin in slightly more than 50 per cent of experimental animals. The reports of finding precipitins to insulin in animals have been inconclusive. However, Tuft,[6] Cannon and Marshall,[7] and Karr and his associates[8] have demonstrated precipitins to insulin in the sera of some of their patients hypersensitive to insulin.

In reviewing the incidence of insulin allergy, one is struck by the wide statistical variations. It is apparent that the variances in these statistical analyses are dependent upon what the individual author considers an allergic reaction. Some consider slight local reactions as important, and others pay attention only to generalized reactions. Joslin and co-workers,[9] in 1922, reported various allergic reactions in four of eighty-three patients. Wilder and his associates,[10] in 1922, reported various allergic reactions in three of forty patients. Murphy, Beardwood, and Miller,[11] in 1934, reported generalized allergic manifestations in two of 940 patients. Allan and Scherer,[12] in 1932, reported statistics from the Mayo Clinic which varied between 3.2 and 13.8 per

cent allergic reactions to insulin. Collens, Lerner, and Fialka,[13] in 1934, reported various allergic reactions in 7.3 per cent of 407 patients. Yasuna[14] reported no generalized insulin reactions in a total of 3,323 diabetic patients at the Boston City Hospital. A review of all the diabetic patients at Mount Sinai Hospital of Cleveland revealed no generalized reactions in over 500 patients.

Those who see any large group of allergic individuals are uniformly impressed by the paucity of diabetics in their clinical population. This supposition has been the source of various theories regarding the diabetic constitution, and Bernstein and his associates[15] pose the question as to whether the latter is antithetic to the allergic constitution or whether the simultaneous appearance of the two traits constitute lethal factors.

Wilmer and Miller,[16] in 1937, studied glucose tolerance curves in allergic individuals and stated that of 5,108 cases in their records, only two of the patients had diabetic symptoms. Beardwood[16] reported two allergic individuals in 1,870 diabetic patients. Swern,[17] in 1931, reported only six patients with diabetes among 4,000 allergic patients. Kern,[18] in a preliminary search, found only one diabetic among 1,600 patients with asthma and hay fever, and this individual proved to be the only asthmatic person among 1,400 diabetic patients. After a more thorough investigation of the subject, Kern found that, although diabetes and allergy rarely occur simultaneously in the same patient, there is a relatively high incidence of positive histories of allergy among diabetic patients.

In reviewing the literature, it is found that reactions rarely occur following the initial injection of insulin. Many reactions occur between the thirteenth and fourteenth day of insulin therapy. In a large number of patients, there had been a lapse of insulin therapy, varying from several months to several years, with sensitivity following resumption of therapy. The similarity of this latent period to the incubation period which characterizes serum sickness has been noted by many authors.

The symptomatology of insulin allergy may be classified into three general types: (1) mild local reactions at the site of injection, (2) severe local reactions at the site of injection, and (3) generalized reactions. In the latter group there is a general or systemic reaction manifested by cutaneous, circulatory, and gastrointestinal symptoms. Urticaria and edema are common and are frequently preceded by numbness, tingling, and intense itching of the involved parts. Swelling of the mucous membrane of the mouth and larynx may occur, causing respiratory embarrassment. Pallor, flushing, and palpitation appear at the onset and may be followed by circulatory collapse with a fall in blood pressure, a low volume pulse, and general prostration. Wechsler and co-workers[19] reported a case in which the patient had symptoms simulating coronary occlusion. Nausea, vomiting, and abdominal cramps are not infrequent accompaniments.

The case to be presented is illustrative of hypersensitivity to insulin protein.

CASE REPORT

Mrs. R., a 60-year-old white female, was referred on Sept. 28, 1940, because of generalized urticaria. Her past history and family history were negative for the allergic disturbances. She was a known diabetic for ten years. In May, 1928, following a cholecystectomy, she was given regular insulin because of a marked hyperglycemia. She was continued on insulin throughout her hospital stay without any apparent local or systemic reactions. After leaving the hospital, she was able to control the diabetes on a well-regulated diet without the use of insulin until the early part of September, 1940, when, because of persistent glycosuria and hyperglycemia, she was sent to the hospital for stabilization of diet and insulin dosage. At this time she had a fasting blood sugar of 280 mg. per 100 c.c., 4 plus glycosuria, and 1 plus acetonuria. Her diet was adjusted to her metabolic requirements, and starting Sept. 17, 1940, she was given protamine zinc insulin, 10 units twice daily, for two days, then 20 units once a day. She noticed an area of induration at the site of insulin injection on Sept. 20. She was discharged from the hospital Sept. 21, 1940, on a basal diet and 20 units of protamine zinc insulin once daily. While at home she noticed increasing local reactions to daily injections of insulin, and on Sept. 24 she had her first episode of generalized urticaria twenty minutes following the injection of insulin of that day. The following day there was a recurrence of urticaria following the insulin injection. On Sept. 26, upon the advice of her physician, she discontinued the use of protamine zinc insulin and changed to regular beef insulin. Almost immediately following the injection of 15 units of the latter, she again had urticaria. On Sept. 27 she took no insulin and had no urticaria. On the morning of Sept. 28 she again took 15 units of regular beef insulin which was shortly followed by severe generalized urticaria.

When I first saw her on the afternoon of Sept. 28, she had no visible urticaria, but did complain of a generalized pruritus and tingling of the skin. Other than a blood pressure of systolic 185 mm. Hg, and diastolic 90 mm. Hg, the physical examination was negative. The urine showed 4 plus sugar and 1 plus acetone.

Intradermal skin tests showed the following reactions as recorded in Table I and shown in Fig. 1: saline control, beef protein, and pork protein were negative; protamine zinc insulin was moderately positive; regular beef insulin was markedly positive; crystalline insulin was moderately positive. Tests to various insulins were all made with approximately 0.02 c.c. of a dilution containing 4 units per cubic centimeter. At this time blood was taken for passive transfer study, the results of which are shown in Fig. 2 and Table I. Regular insulin, markedly positive; protamine zinc insulin and crystalline insulin,

moderately positive. The patient was hospitalized for further study and desensitization to insulin.

Crystalline insulin was chosen for this latter purpose, and as shown in Table II, starting with 0.1 unit and increasing the amount of insulin by small increments, an interval of twenty minutes was allowed between the first and second injection, thirty minutes between subsequent injections for seven doses, and further injections at less frequent intervals. It was noticed, that following each injection of insulin, there was some local reaction which gradually increased in size as the insulin dose increased. After a total of 23 units of insulin had been given, the patient

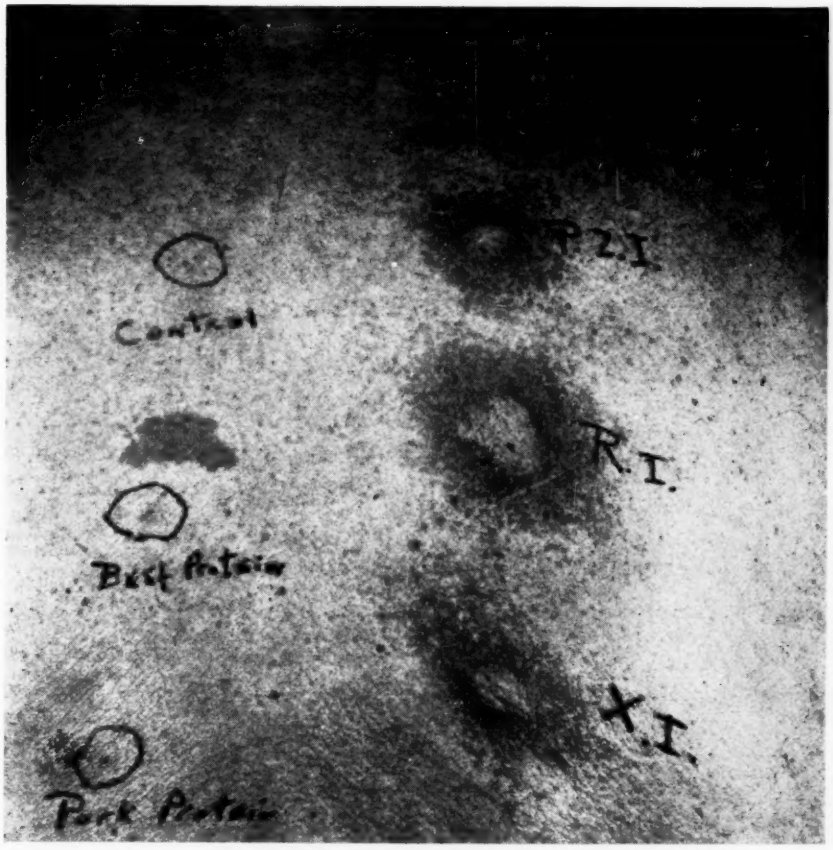

Fig. 1.—Direct Skin Reactions to Insulin in Case Cited. Tests to various insulins were all made with approximately 0.02 c.c. of a dilution containing 4 units per cubic centimeter. *R.I.*, Regular insulin; *P.Z.I.*, protamine zinc insulin; *X.I.*, crystalline insulin.

developed severe generalized urticaria which required the injection of 8 minims of adrenalin, 1:1,000, for relief. She then was given an overnight rest period of twelve hours, following which insulin administration was again started with 4 units of insulin, three times daily. Following the evening dose, there was some slight urticaria. On the

second day, 6 units, twice daily, were given. Following the afternoon insulin dose of the second day, she again developed urticaria. The dosage of insulin was then decreased to 4 units twice daily, then increased to 6 units twice daily, then 8 units twice daily, then increased to 6 units twice daily, then 8 units twice daily, and finally, 10 units twice daily, without any further urticarial reactions. She was maintained on this latter dose of insulin throughout the balance of her hospital stay.

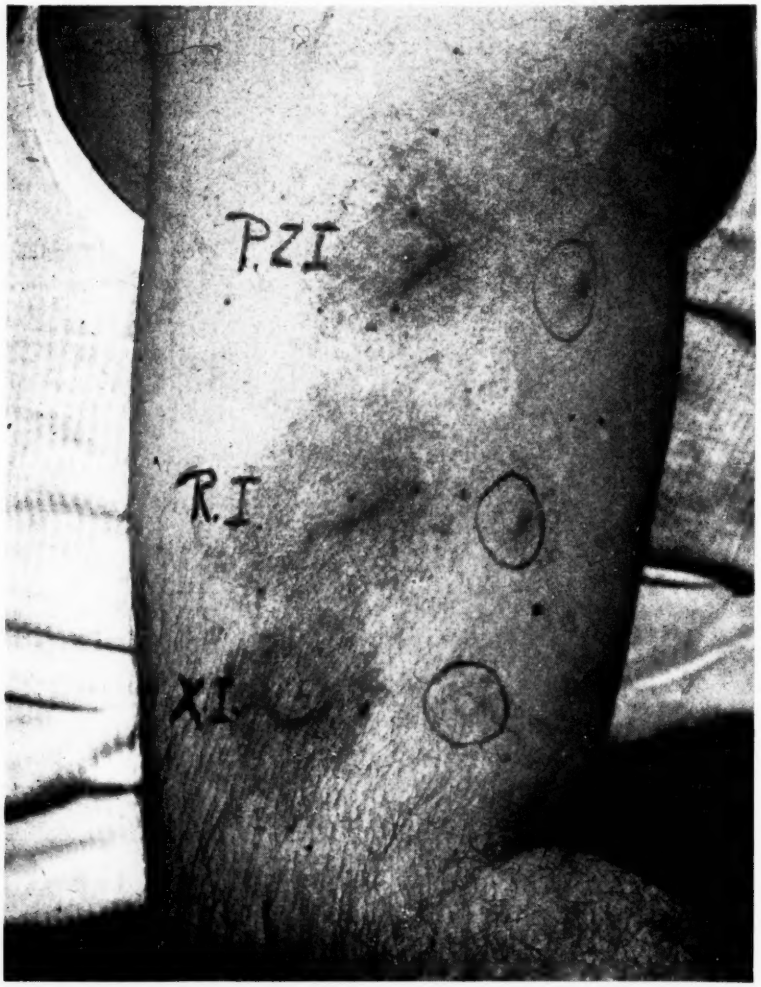

Fig. 2.—Reactions to Insulins in Sites Passively Sensitized by Serum of Patient in Case Cited. Tests to various insulins were all made with approximately 0.02 c.c. of a dilution containing 4 units per cubic centimeter. *R.I.*, Regular insulin; *P.Z.I.*, protamine zinc insulin; *X.I.*, crystalline insulin.

Since her discharge from the hospital, she has been able to decrease the amount of insulin to 10 units daily. On several occasions throughout the past year, she has changed from crystalline insulin to regular beef and pork insulin without any untoward reactions. Direct skin tests and passive transfer studies are as recorded on Table I.

TABLE I

DIRECT AND PASSIVE TRANSFER SKIN REACTIONS

DATE	DIRECT SKIN TESTS							PASSIVE TRANSFER		
	R.I.	P.Z.I.	X.I.	CONTROL	BEEF	PORK	PROTAMINE	R.I.	P.Z.I.	X.I.
9/28/40	Mkd.	Mod.–	Mod.+	0	0	0		Mkd.	Mod.	Mod.
9/30/40	Mkd.	Mod.–	Mod.	0	0	0	0			
11/ 1/40	Mod.	Mod.	Mkd.					Mod.	Mod.	Mod.
11/20/40	Mod.	Sl.+	Mod.–							
12/17/40	Sl.	Sl.	Mod.					Sl.	Sl.	Sl.+
1/13/41	Sl.	Sl.	Sl.							
3/ 4/41	0	0	0					0	0	0
5/ 8/41	0	0	0					0	0	0
7/25/41	0	0	0							

Tests to various insulins were all made with approximately 0.02 c.c. of a dilution containing 4 units per cubic centimeter.

R.I., Regular insulin; P.Z.I., protamine zinc insulin; X.I., crystalline insulin.

TABLE II

METHOD OF DESENSITIZATION USED

DATE	TIME	INSULIN UNITS	REACTION	URINE		BLOOD	ADRENALIN (MINIMS)
				SUGAR	ACETONE		
10/ 3/40	11:00 A.M.	0.1	Wheal 2 sq. cm.	4+	0	306	
	11:20 A.M.	0.1	Wheal 4 sq. cm.				
	11:50 A.M.	0.2	Wheal 4 sq. cm.				
	12:20 P.M.	0.4	Wheal 6 sq. cm.				
	12:50 P.M.	0.6	Wheal 6 sq. cm. with induration				
	1:20 P.M.	0.8	Induration, slight				
	1:50 P.M.	1.2	Induration, slight				
	2:20 P.M.	1.6	Induration, moderate				
	2:50 P.M.	2.0	Induration, marked				
	6:00 P.M.	2.4	Induration, marked	4+	0		
	6:30 P.M.	2.8	Induration, marked				
	7:00 P.M.	3.2	Induration, marked				
	7:30 P.M.	3.6	Urticaria, slight				
	8:00 P.M.	4.0	Urticaria, marked	4+	0		5×2
10/ 4/40	8:30 A.M.	4.0		4+	0	267	
	12:45 P.M.	4.0					
	5:15 P.M.	4.0	Urticaria	4+	0		5
10/ 5/40	8:00 A.M.	6.0		4+	0	254	
	12:00 noon	6.0	Urticaria, slight	4+	0		3
10/ 6/40	8:00 A.M.	4.0		4+	0		
	12:00 noon	4.0	Urticaria, slight	4+	0		3
10/ 7/40	8:00 A.M.	4.0		4+			
	5:00 P.M.	4.0	Urticaria, slight	4+			
10/ 8/40	8:00 A.M.	6.0	Negative	4+		240	
	5:00 P.M.	6.0	Negative	4+			
10/ 9/40	8:00 A.M.	8.0	Negative	3+			
	5:00 P.M.	8.0	Negative	3+			
10/10/40	8:00 A.M.	10.0	Negative	2+		188	
	5:00 P.M.	10.0	Negative	2+			
10/11/40	8:00 A.M.	10.0	Negative	Trace			
	5:00 P.M.	10.0	Negative	1+			
10/12/40	8:00 A.M.	10.0	Negative	0		124	
	5:00 P.M.	10.0	Negative	0			

SUMMARY

1. A case illustrative of hypersensitivity to insulin protein with positive direct skin reactions and passive transfer reactions has been presented.

2. The similarity in this case between insulin allergy and serum sickness has been brought out; namely, an absence of atopic predisposition, the tendency toward a latent period, the type of symptoms, and the appearance of reagins which were not of prolonged duration.

3. Desensitization to insulin was effected, as evidenced by cessation of the patient's symptoms with continued use of various types of insulin; the inability to further demonstrate direct positive skin reactions to insulin; and the disappearance of reagins to insulin as evidenced by the inability to demonstrate further passive transfer reactions.

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DETECTION OF THE "THERMOSTABLE" ANTIBODY BY MEANS OF THE PRECIPITIN REACTION

Preliminary Report

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THE reason for clinical improvement in patients with hay fever who have been treated with specific pollen extracts has been the subject of particular study during the past several years. The work of Cooke and his associates[1] who found a difference in the reactions of blood serum taken from patients before and after specific pollen therapy is well known. Cooke's inference that serum from treated patients contained what he termed a "blocking antibody" was further investigated by Loveless.[2] This investigator demonstrated that the blocking antibody was actually a neutralizing antibody. She distinguished this from reagin which is thermolabile by its heat-resisting capacity, among other qualities, and designated it the "thermostable antibody."

Both Cooke and Loveless, as well as all other investigators who have published reports on this subject,[3-6] have depended on the technique of passive transfer of the serum to be studied to sites on normal skin. Although this test so widely used both clinically and immunologically presents little difficulty in its performance, it is not well suited to delicate titrations. The inherent errors of the method are several and not easily controlled, and unless one is greatly experienced, it is difficult to read small gradations of presenting reactions. Moreover, Loveless pointed out that there may be clinical application in the determination of thermostable antibody in relation to the amount of treatment required. We also have been occupied with this problem. If it proves to be valid, a simple technique for titration of antibody available to anyone trained in conventional immunologic methods, other than that of passive transfer, would seem necessary. Moreover, a simple method would permit further investigation of the thermostable antibody. The primary purpose of this investigation was to develop such a method, which seemed possible if a potent antiragweed rabbit serum could be produced.

Ragweed extract, although a strong atopen in man, is a weak antigen for the development of antibodies in animals. After considerable trial and error, the following method was adopted.

METHODS

Low ragweed pollen was freshly extracted with a solution of 0.5 per cent sodium chloride and 0.3 per cent sodium bicarbonate. The extract

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was evaporated in a dializing sac by means of a fan to a concentration of 2.5 mg. of nitrogen per cubic centimeter. The proteins were precipitated with aluminum hydroxide cream prepared according to the method of Welker and Tracy.[7] Rabbits were injected with 30 c.c. of this suspension by the technique of Welker and Hektoen[8] wherein deposits were made intramuscularly at several sites. The animals were bled after two weeks and at weekly intervals thereafter. Precipitation tests were carried out in the usual manner by incubating for one hour equal parts of rabbit serum with dilutions of ragweed extract. Turbidity was noted and final readings of precipitates made the following day after the tubes had remained in the icebox overnight. This serum was

TABLE I

PRECIPITIN TESTS WITH MIXTURES OF ANTIRAGWEED RABBIT SERUM AND OF A AND P SERA EACH EXPOSED TO RAGWEED EXTRACT

PATIENT	SERUM	CONCENTRATIONS OF RAGWEED EXTRACT IN PROTEIN NITROGEN UNITS							
		2,500	1,250	625	312	156	78	40	20
Ba	A	4+	4+	4+	4+	3+	1+	0	0
	P	2+	2+	0	0	0	0	0	0
La	A	4+	4+	4+	4+	4+	2+	0	0
	P	4+	3+	0	0	0	0	0	0
St	A	4+	4+	4+	3+	3+	1+	1+	0
	P	4+	3+	2+	0	0	0	0	0
Wa	A	4+	4+	4+	4+	3+	1+	0	0
	P	4+	4+	3+	2+	1+	0	0	0
Qu	A	4+	4+	4+	3+	1+	0	0	0
	P	4+	4+	3+	2+	1+	0	0	0
Sh	A	4+	4+	4+	4+	1+	0	0	0
	P	4+	3+	1+	0	0	0	0	0
Vo	A	4+	4+	4+	2+	1+	0	0	0
	P	4+	2+	1+	0	0	0	0	0
Am	A	4+	4+	4+	4+	3+	2+	1+	0
	P	4+	4+	4+	4+	2+	1+	0	0
Ge	A	4+	4+	4+	4+	3+	2+	1+	0
	P	4+	4+	2+	2+	1+	0	0	0
Bl	A	4+	4+	4+	2+	1+	0	0	0
	P	4+	4+	4+	3+	0	0	0	0
Ca	A	4+	4+	3+	3+	1+	1+	0	0
	P	4+	4+	3+	2+	0	0	0	0
Sh	A	3+	4+	4+	2+	1+	0	0	0
	P	4+	2+	0	0	0	0	0	0
Fa	A	4+	4+	4+	4+	2+	1+	0	0
	P	4+	4+	4+	4+	1+	0	0	0
Ta	A	4+	4+	3+	3+	2+	1+	0	0
	P	4+	3+	3+	0	0	0	0	0
Am	A	4+	4+	4+	4+	3+	2+	1+	0
	P	4+	4+	4+	4+	2+	1+	0	0

used in testing for thermostable antibody recorded in Table I. It required more than 25,000 units of ragweed extract for precipitin saturation.*

Sera from fifteen patients with ragweed hay fever taken before treatment (A serum) and after treatment (P serum) were tested as follows. All sera were heated to 56° C. for four hours, thereby destroying the thermolabile antibody contained in each. Equal parts (0.25 c.c.) of heated A serum and 20,000 units of low ragweed extract were mixed by thorough shaking and allowed to stand at icebox temperatures overnight. Dilutions of this mixture were then made so that the final range of concentration of antigen when mixed with rabbit serum was 2,500 to 20 protein nitrogen units. P serum was similarly treated.

Equal parts (0.25 c.c.) of the mixtures of A and of P sera with ragweed extract were mixed with antiragweed rabbit serum, thoroughly shaken in an automatic shaker for two minutes and incubated at 37° C. for one hour. Turbidity in each tube was recorded. Final readings were made after the tubes had remained at icebox temperatures overnight. For controls, antiragweed rabbit serum alone, A and P, antigen mixtures, antigen alone, and mixtures of rabbit serum and antigen were used.

Control tests showed no precipitation except with rabbit serum and antigen.

DISCUSSION

From this small series of available cases, it is apparent that, with one or two possible exceptions, more precipitation occurred with dilutions of ragweed antigen and heated A serum than with similar mixtures of P serum when each was mixed with antiragweed rabbit serum. This result indicates that more ragweed extract was available in the A serum mixtures than in the P serum mixtures for precipitins to act upon. Evidently P serum had neutralized some of the ragweed extract, which was thus not free to contact precipitins present in the mixture.

This report is entirely preliminary. Further work is in progress in standardizing antiragweed rabbit serum. With this at a given strength and ragweed extract in constant units, variations in the neutralizing capacity of P serum should be more clearly determined.

The precipitin method was compared to that of passive transfer for the detection of thermostable antibody. Dilutions of heated A and P sera, antigen mixtures were tested on sites in normal skin previously sensitized with ragweed A serum. The reactions obtained were contrasted to those of similar dilutions of these mixtures precipitated with antiragweed rabbit serum. The two methods compared favorably in

*In more recent experiments the following modification in the preparation of antiragweed rabbit serum was made. Staphylococcus toxin (Sharp & Dohme, Inc., minimum lethal dose in mice 0.01 c.c.) in doses of 0.05 c.c. was given subcutaneously ten days after the first injection of antigen and the animals bled one week later. Thereby a considerably more potent serum was obtained.

their results. However, the precipitin method produces sharper end points and because of its relative simplicity is available to anyone trained in conventional immunologic technique.

SUMMARY

1. A precipitin method for the detection of thermostable antibody has been devised.

2. This method compares favorably with that of passive transfer and is simple to perform.

3. This report is preliminary.

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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

II. Mold Extracts—A Statistical Study

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A COOPERATIVE study of molds and their relationship to allergic respiratory diseases was organized in 1939 between the Department of Botany and Bacteriology of The University of Texas and a group of physicians organized as the Association of Allergists for Mycological Investigation.[1] This organization was brought into being largely through the efforts of Dr. Homer E. Prince of Houston, Texas. Its existence at the present time is due to the enormous amount of work done by Dr. Prince and by Dr. Marie B. Morrow and Mr. E. P. Lowe of The University of Texas. The results of my studies with extracts obtained from this cooperative study are here presented.

SOURCE OF MOLDS, METHODS OF GROWING, AND PREPARATION OF EXTRACTS

The source, method of growing, distribution, and identification of the molds have been described by Morrow, Lowe, and Prince.[1] The preparation of the extracts has been described by Prince and Morrow.[2] The extracts were furnished by Prince to all members of the Association of Allergists for Mycological Investigation. For this study, a 1:5,000 dilution was used for intracutaneous testing.

EXTRACTS

Thirty-three extracts of individual species and five mixed extracts were used for this study. The mixed extracts were: (1) mixed Penicillium, 8 species; (2) mixed Aspergillus, 5 species; (3) mixed Curvularia, 2 species; (4) mixed Alternaria, 2 species; and (5) mixed Hormodendrum, 3 species.

METHODS OF STUDY

Asthma and hay fever patients were tested with a 1:5,000 dilution of the extracts listed in Table I. At the same time, another group of patients, in whom there were no symptoms of asthma, hay fever, sinus disease, or other respiratory disorders, was tested with the same extracts in the same dilution (Table I). Both groups were taken from ambulatory patients in private practice. In this latter group, that is, the controls, I had some allergic patients as well as some nonallergic patients. It was pointed out by Efron[3] that a control series of this type

Read at the Annual Meeting of the American Association for the Study of Allergy, Atlantic City, June 8, 1942.

TABLE I

NAME OF MOLD		TOTAL	NEGATIVE	POSITIVE	P†	DIAGNOSTIC EFFICIENCY (%)	COMMENT
Alternaria BC-30*	Control	237	188	49	Less than 0.01	61.4	Very poor extract; no clinical value
	Asthma and Hay fever	327	219	108			
Alternaria "B," species B SA-19	Control	203	157	46	Less than 0.01	58.8	Extract of no clinical value
	Asthma and Hay fever	293	198	95			
Alternaria, mixed MA-9, H-9	Control	72	58	14	Above 0.05		Extract is an irritant
	Asthma and Hay fever	110	80	30			
Alternaria tenuis B-27	Control	179	159	20	Less than 0.01	65.1	100 positive tests yield 65 of clinical significance; poor
	Asthma and Hay fever	249	197	52			
Aspergillus BC-3B	Control	236	184	52	Less than 0.01	58.0	Extract of no clinical value
	Asthma and Hay fever	329	229	100			
Aspergillus flavus link W-48	Control	124	110	14	Above 0.05		Extract is an irritant
	Asthma and Hay fever	187	154	33			
Aspergillus, mixed W-49, B-10, B-72, R-17, W-48	Control	83	74	9	Less than 0.01	70.7	Out of 100 positive tests, only 70 will have diagnostic significance
	Asthma and Hay fever	115	85	30			
Aspergillus niger B-10	Control	150	126	24	Above 0.05		Extract is an irritant
	Asthma and Hay fever	243	203	40			
Aspergillus terrus W-49	Control	139	113	26	Above 0.05		Extract is an irritant
	Asthma and Hay fever	218	163	55			
Basisporium gallarum SW-20	Control	241	185	56	Above 0.05		Extract is an irritant
	Asthma and Hay fever	329	232	97			
Botrytis SA-14	Control	84	74	10	Less than 0.05	66.8	Very poor extract; practically no clinical value
	Asthma and Hay fever	113	86	27			
Curvularia, mixed P-5, BC-1	Control	86	79	7	Less than 0.05	72.8	Has some diagnostic significance but not a good extract
	Asthma and Hay fever	115	90	25			
Curvularia speciferia Boedijn SA-9	Control	335	292	43	Less than 0.01	62.2	Extract very poor; very little clinical value
	Asthma and Hay fever	482	380	102			
Curvularia trifolii Boedijn P-5	Control	148	134	14	Above 0.05		Extract is an irritant
	Asthma and Hay fever	230	177	53			

*Numbers used for identification by the Association of Allergists for Mycological Investigation.

†The probability was calculated by means of the Chi-Square statistic.

TABLE I—CONT'D

NAME OF MOLD		TOTAL	NEGATIVE	POSITIVE	P†	DIAGNOSTIC EFFICIENCY (%)	COMMENT
Fusarium species A BC-40	Control	80	57	23	Above 0.05		Extract is an irritant
	Asthma and Hay fever	109	64	45			
Gliocladium penicilloides S-20	Control	77	64	13	Above 0.05		Extract is an irritant
	Asthma and Hay fever	107	77	30			
Helmenthosporium halodes Dreschler SA-6	Control	154	140	14	Less than 0.01	67.7	Extract of very little clinical value
	Asthma and Hay fever	235	190	45			
Helmenthosporium, mixed SA-6, WA-28	Control	79	71	8	Above 0.05		Extract is an irritant
	Asthma and Hay fever	115	80	35			
Hormodendrum P-1	Control	199	160	39	Less than 0.01	58.3	Extract of no clinical value
	Asthma and Hay fever	292	212	80			
Hormodendrum "B" R-15	Control	146	122	24	Above 0.05		Extract is an irritant
	Asthma and Hay fever	227	159	68			
Hormodendrum eladosporoides W-16	Control	168	146	22	Less than 0.01	64.2	Very poor extract; no clinical value
	Asthma and Hay fever	243	185	58			
Hormodendrum, mixed W-13, P-1, R-15	Control	77	61	16	Above 0.05		Extract is an irritant
	Asthma and Hay fever	116	80	36			
Monilia niger R-40	Control	164	145	19	Less than 0.01	67.0	Very poor extract; very little clinical value
	Asthma and Hay fever	226	173	53			
Mycogone SW-21	Control	85	73	12	Less than 0.05	65.0	Very poor extract; very little clinical value
	Asthma and Hay fever	122	90	32			
Paecilomyces B-34	Control	80	73	7	Less than 0.05	70.9	Has some diagnostic significance but not a good extract
	Asthma and Hay fever	112	88	24			
Paecilomyces varioto P-48	Control	195	165	30	Less than 0.01	65.5	Very poor extract; very little clinical value
	Asthma and Hay fever	283	200	83			
Penicillium carminoviolaceum W-7	Control	208	155	53	Less than 0.01	60.1	Very poor extract, no clinical value
	Asthma and Hay fever	271	167	104			
Penicillium intricatum Thom BC-18	Control	167	147	20	Less than 0.05	66.3	Very poor extract; very little clinical value
	Asthma and Hay fever	235	180	55			

TABLE I—CONT'D

NAME OF MOLD		TOTAL	NEGATIVE	POSITIVE	P†	DIAGNOSTIC EFFICIENCY (%)	COMMENT
Penicillium, mixed BC-18, W-15, MA-12, W-7, P-77, S-17, W-2, SB-11, MA-4	Control	94	81	13	Above 0.05		Extract is an irritant
	Asthma and Hay fever	128	102	26			
Penicillium monoveryicilliate W-2, W-15	Control	431	376	55	Less than 0.01	66.1	Very poor extract; practically no clinical value
	Asthma and Hay fever	579	435	144			
Penicillium notatum MA-12	Control	175	139	36	Above 0.05		Extract is an irritant
	Asthma and Hay fever	246	201	45			
Pycnidal P-62	Control	83	71	12	Above 0.05		Extract is an irritant
	Asthma and Hay fever	103	82	21			
Pycnidal species P-55	Control	156	133	23	Less than 0.05	63.3	Extract very poor; very little clinical value
	Asthma and Hay fever	234	175	59			
Rhizopus nigricans SA-4	Control	249	206	43	Less than 0.01	62.9	Extract very poor; very little clinical value
	Asthma and Hay fever	284	201	83			
Spondylocladium WA-26	Control	270	197	73	Less than 0.01	60.8	Very poor extract
	Asthma and Hay fever	398	232	166			
Stemphylium botryosum MA-28	Control	232	203	29	Less than 0.01	68.0	Very poor extract; practically no clinical value
	Asthma and Hay fever	336	247	89			
Sterile mycelium M-5	Control	248	214	34	Less than 0.01	66.1	Very poor extract; practically no clinical value
	Asthma and Hay Fever	378	277	101			
Unidentified S-1	Control	174	153	21	Less than 0.01	68.5	Very poor extract; practically no clinical value
	Asthma and Hay fever	291	214	77			

should be made up of individuals who have no symptoms attributable to allergic disease. He pointed out that there is a possibility of the occurrence of nondiagnostic specific skin reactions in patients who have allergic disease. Consequently, ten of the best extracts were selected from Table I and tested on a group of 144 healthy individuals who gave a negative history of asthma, hay fever, urticaria, and eczema. This group was made up of nurses and college students (Table II).

STATISTICAL ANALYSIS

By statistical analysis, it was found that fourteen, or 37 per cent, of the extracts had given reactions that could be accounted for by the ir-

TABLE II

NAME OF MOLD		TOTAL	NEGATIVE	POSITIVE	P*	DIAGNOSTIC EFFICIENCY (%)	COMMENT
Alternaria SA-19	Control	144	116	28	Less than 0.01	62.5	Extract of very little clinical value
	Asthma and Hay fever	293	198	95			
Aspergillus, mixed W-49, B-10, B-72, R-17, W-48	Control	144	126	18	Less than 0.01	67.6	Extract of very little clinical value
	Asthma and Hay fever	115	85	30			
Botrytis SA-14	Control	144	124	20	Less than 0.05	63.2	Extract of very little clinical value
	Asthma and Hay fever	113	86	27			
Curvularia speciferia SA-9	Control	144	126	18	Less than 0.05	62.9	Extract of very little clinical value
	Asthma and Hay fever	482	380	102			
Monilia niger R-40	Control	144	123	21	Less than 0.05	61.7	Very poor extract
	Asthma and Hay fever	226	173	53			
Mycogone SW-21	Control	144	121	23	Less than 0.05	62.1	Extract of very little clinical value
	Asthma and Hay fever	122	90	32			
Paecilomyces B-34	Control	144	129	15	Less than 0.05	64.1	Extract of very little clinical value
	Asthma and Hay fever	112	88	24			
Penicillium intricatum BC-18	Control	144	124	20	Less than 0.05	62.7	Extract of very little clinical value
	Asthma and Hay fever	235	180	55			
Pycnidal species P-55	Control	144	128	16	Less than 0.01	69.4	Has some diagnostic significance but not a good extract
	Asthma and Hay fever	234	175	59			
Stemphylium botryosum MA-28	Control	144	128	16	Less than 0.01	70.5	Has some diagnostic significance but not a good extract
	Asthma and Hay fever	336	247	89			

*The probability was calculated by means of the Chi-Square statistic.

ritant properties of the extracts. The diagnostic efficiency of the extracts which were nonirritant was computed according to the formula given by Efron, Boatner, Pabst, and Feibleman.[4] It was found that only three of the twenty-four nonirritant extracts gave a diagnostic efficiency as high as 70 per cent. This means that of 100 positive tests in patients whose symptoms could be due to fungi, only seventy will have any diagnostic significance. Most of the nonirritant extracts showed about 60 per cent diagnostic efficiency, which means that the chances of a positive reaction having clinical significance with these extracts are not much greater than one could guess. The diagnostic efficiency of the irritant extracts was not calculated, since it is not possible to calculate such efficiency of irritant extracts. In Table II, where controls who had no symptoms attributable to allergic disease were used, the results were about the same as those obtained in the first series (Table I).

TABLE III

MOLDS	NUMBER OF PATIENTS	MODERATE REACTIONS		MOD.-MKD., MARKED REACTIONS		TOTAL REACTIONS
		NO.	PER CENT	NO.	PER CENT	PER CENT
Alternaria BC-30	327	56	17.1	52	15.9	33.0
Alternaria "B," species B SA-19	293	31	10.6	64	21.8	32.4
Alternaria, mixed MA-9, H-9	110	18	16.4	12	10.9	27.3
Alternaria tenuis B-27	249	27	10.8	25	10.0	20.8
Total	979	132	13.5	153	15.6	29.1

TABLE IV

MOLDS	NUMBER OF PATIENTS	MODERATE REACTIONS		MOD.-MKD., MARKED REACTIONS		TOTAL REACTIONS
		NO.	PER CENT	NO.	PER CENT	PER CENT
Aspergillus BC-3B	329	60	18.2	40	12.2	30.4
Aspergillus flavus link W-48	187	22	11.8	11	5.9	17.7
Aspergillus, mixed W-49, B-10, B-72, R-17, W-48	115	4	3.5	26	22.6	26.1
Aspergillus niger B-10	243	32	18.2	8	3.3	21.5
Aspergillus terrus W-49	218	40	18.4	15	6.9	25.3
Total	1092	158	14.5	100	9.2	23.7

TABLE V

MOLDS	NUMBER OF PATIENTS	MODERATE REACTIONS		MOD.-MKD., MARKED REACTIONS		TOTAL REACTIONS
		NO.	PER CENT	NO.	PER CENT	PER CENT
Hormodendrum "B" R-15	227	42	18.5	26	11.5	30.0
Hormodendrum cladosporoides W-16	243	34	14.0	24	9.9	23.9
Hormodendrum, mixed W-13, P-1, R-15	116	11	9.5	25	21.6	31.1
Hormodendrum P-1	292	37	12.7	43	14.7	27.4
Total	878	124	14.1	118	13.4	27.5

INCIDENCE OF SKIN REACTIONS TO AIR-BORNE MOLDS

The group of Alternaria extracts gave 29 per cent positive reactions (Table III). The individual extracts gave positive reactions varying from 20.8 to 33 per cent. Chobot, Dundy, and Schaffer[5] reported 28.2 per cent positive reactions in a series of 117 adult cases.

TABLE VI

MOLDS	NUMBER OF PATIENTS	MODERATE REACTIONS		MOD.-MKD., MARKED REACTIONS		TOTAL RE-ACTIONS
		NO.	PER CENT	NO.	PER CENT	PER CENT
Penicillium carmino-violaceum W-7	271	45	16.6	59	21.8	38.4
Penicillium intricatum Thom BC-18	235	43	18.3	12	5.1	23.4
Penicillium, mixed W-2, SB-11, BC-18, W-15, MA-12, W-7, P-77, S-17, MA-4	128	13	10.2	13	10.2	20.4
Penicillium monoveryicil-liate W-2, W-15	579	86	14.9	58	10.0	24.9
Penicillium notatum MA-12	246	12	4.9	33	13.4	18.3
Total	1459	199	13.6	175	11.9	25.5

Aspergillus, all extracts, gave 23.7 per cent positive reactions (Table IV). Individual extracts gave positive reactions varying from 17.7 to 30.4 per cent. Chobot and his associates,[5] in a series of 117 adult cases, found 16.1 per cent positive reactions.

The group of Hormodendrum extracts gave 27.5 per cent positive reactions (Table V). The individual extracts gave from 23.9 to 31.1 per cent positive reactions. Chobot and his associates,[5] in a series of 115 adult cases, obtained 20.8 per cent positive reactions.

The group of Penicillium extracts gave 25.5 per cent positive reactions and the individual extracts gave positive reactions varying from 18.3 to 38.4 per cent (Table VI). Chobot,[5] in a series of 117 adult cases, obtained 19.6 per cent positive reactions.

These figures, when studied in connection with Table I, will serve to emphasize that positive reactions alone have no significance unless controls have been run and the extract can be defined in biologic terms, as has been repeatedly pointed out by Efron and his associates.[4, 6-11]

SUMMARY

1. By statistical analysis, it is shown that 37 per cent of a series of thirty-eight mold extracts were irritants and of no clinical value. Of the remaining twenty-four extracts, only three had a diagnostic efficiency as high as 70 per cent. Most of the extracts had an efficiency of about 60 per cent which is not much better than one could expect.

2. The incidence of skin reactions to extracts of air-borne molds is presented and, when studied in relation to the irritant qualities of the extracts and the diagnostic efficiency of the extracts, it emphasizes the importance of using efficient statistics for the analysis of biologic data.

3. Had efficient statistics been applied to our extracts in 1940, we could have saved at least two years' time with the present studies and devoted this energy to the preparation of better extracts.

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DISCUSSION

DR. H. E. PRINCE, Houston.—There are several reasons, I think, why we have all been somewhat uncertain in evaluating mold antigens. In the first place, molds have become of known clinical importance only recently. In those areas of clear-cut seasons such as exist in the northern section of the country, molds have been more obviously associated with forms of seasonal symptoms not explainable by any pollen or other inhalant sensitivity. In cases with perennial or erratic distribution, however, particularly in the South where unusual seasonal overlapping occurs, the etiologic importance of molds has been more obscure. The attitude of the clinician in a great many instances, often of necessity, has not been one of selecting positive allergens coinciding with clinical symptoms and excusing therapeutic failures on shortcomings and pitfalls of our methods of treatment. Instead, in desperate hope of relieving obstinate and obscure cases, he has been forced to resort to a therapeutic trial of anything giving positive skin tests, and which might occur among the possible contacts, to explain the symptoms. It is not surprising, then, that mold antigens have been variously evaluated.

For several years I have been aware that many mold extracts in my hands were quite reactive, and I have thought that many reactions were of the irritative class.

My first impressions with mold extracts were that with them reactions frequently could be obtained after other studies proved fruitless. It soon was difficult, however, particularly as many molds were added to the testing tray, to distinguish between the really important reactions and those which were purely irritative. At first I did mold testing entirely by the intradermal method, using 1:5,000 or 1:1,000 dilutions. Still not certain in interpreting reactions, I have within the past few years employed scratch or punch testing with concentrated extracts in preliminary studies, and have followed this with 1:100 or 1:1,000 dilutions intra-

dermally. I believe that 1:100 testing will give a great many small and probably false positive reactions with a variety of molds, but when strongly positive tests are obtained with a few molds in 1:100 strength and can be maintained in 1:1,000 or weaker dilutions, their diagnostic significance is increased, and as weaker titrating tests are carried out, the confusing reactions will disappear. I have attached great significance to reactions grouped among botanical relatives, particularly in the dematiaceous forms. On the other hand, it frequently happens in our practice that reactions are erratic or at least not confined to botanical groups, and even after titrating with weaker strengths we remain confused. For several years I have attempted to check by passive transfer all these cases, employing all the molds and any other inhalants or pollens that are suggested in direct skin testing. I have been impressed by two findings: First, in a high percentage of the patients with confusing mold tests, passive transfer will reveal largely negative findings; second, when mold tests occur among botanical groups, they frequently react positively by passive transfer, and initially positive tests from unrelated forms are frequently negative on transfer. By selecting molds for therapy that most consistently show definitely positive reactions on scratch, weaker titrations, and passive transfer, our mold therapy has been definitely more encouraging. Provocative testing has been employed rarely to confirm positive reactions.

It seems obvious, therefore, that with our technique of preparation, certain mold extracts are irritating and require an effort at exclusion before they can assume diagnostic importance. This applies in particular to the dematiaceous forms and to occasional unrelated molds. On the other hand, the aspergilli and penicilli and some others are either of very little clinical importance or we have not extracted them properly, because they are largely reactive only in the irritative dilutions mentioned above. Inasmuch as many of these latter forms have been found in our survey to be rather widely distributed, it is premature at this time to assume their nonimportance. With the thought of preparing more potent and less irritating mold extracts, it was decided at the Little Rock meeting of the mold group to discontinue plate exposures at most of the old stations in the survey and devote more effort to technique of antigen production and animal experimentation. We shall probably have more to say about this at a later date.

I have checked back on the extracts Dr. Browning used in his studies, and I believe most of them were prepared in 1939 or early in 1940. At that time extractions were made with normal saline containing 1:10,000 merthiolate. These extracts seemed to deteriorate rather rapidly, and in late 1940 Hollister-Stier solution was substituted as an extracting fluid. Some molds were defatted, others were not. It is quite possible that the extracts had deteriorated somewhat by the time they were used in the studies.

Dr. Browning has made an extensive study with mold extracts. His comparisons with other published reports suggest that our extracts compare favorably with extracts prepared elsewhere. If we are to presume that such analysis as this is a means of determining the diagnostic dependability of any extract, then his findings further corroborate the impressions that mold extracts as presently employed are inadequate. If extracts can be improved, there is a distinct possibility that mold allergy might be even more commonly recognized than is now suspected.

I would like to ask Dr. Browning what information he has obtained in applying such analysis as he has reported to pollens or other extracts.

DR. SAMUEL M. FEINBERG, Chicago.—At Little Rock I had occasion to hear some of the results cited in Browning's paper today. Naturally it disturbed me a great deal because I had the impression that in our diagnostic work with mold extracts, the results were much more findable and conclusive. So, when I came back I got busy on my records from the office, and tabulated some figures on a series of about 600 patients, not all mold allergy, of course, but 600 patients as they came into the office over a period of time.

I divided these patients into two main groups: Group I was made up of patients whom we were quite certain clinically were allergic to fungi. We were certain by virtue of definite criteria in the history and by subsequent observation. If the patients did not meet those requirements, we did not use them in that category.

Group II contained patients whom we had reason to believe had no evidence of clinical mold allergy. They were patients with urticaria, angioneurotic edema, migraine, gastrointestinal allergy, infectious asthma, pure seasonal hay fever, particularly of the autumnal variety, and chronic vasomotor rhinitis.

We realize that type of classification might be impossible in the South because they have a little different problem there, but we can do it in our territory.

We can or should be able to recognize a mold case clinically. It has been my custom for a long time to commit myself in writing, on the chart, before I test a patient, "this patient probably is a mold allergic." I am correct most of the time, as far as skin tests are concerned, subsequently.

Might I say, also, that as far as the skin tests are concerned, the results I will show you on a table are mostly on the basis of scratch tests, either with concentrated extracts or with the actual dry powder. Only very few were on the basis of intracutaneous tests, and only then, if there were very decided reactions, did we include them in that category.

(*Slide.*)

In the first group, those having clinical mold allergy, there were 253 patients; 241 were positive and 12 were negative, a percentage of 96 per cent positive.

The second group, clinically not mold allergy (nonrespiratory cases, infectious asthma, fall pollinosis, and respiratory allergy), totaled 351 patients; only 10 were definitely positive, a percentage of 3.

If I ever had any doubt about the diagnostic significance of these tests with the proper materials in mold allergy, I certainly dismissed them from my mind after I got the figures. I had never arranged the data in that way.

You might say, "Why were some negative in the clinical mold allergy cases? That is an additional problem that we have. It remains to be solved. We do not know. We understand in the South there are many more of that type that behave as mold cases but are negative to test.

You might also question my enthusiasm with respect to fungi, because of the high incidence of mold allergy in a group of about 600 cases. Personally, I do not believe that this incidence is actually as it exists in our territory, but it so happens that a large percentage of those patients who had had diagnostic and therapeutic failures in the past owed their failures to the fact that mold allergy was not seriously considered in their diagnosis. Therefore, these statistics are high as far as the general incidence of clinical mold cases of allergy is concerned.

I believe, then, that either in the South there is a different situation, or different molds, or that better methods of preparing antigens should be employed in order to get these types of results.

DR. I. S. KAHN, San Antonio.—Attention has been called to the existence of intradermal, positive skin tests, especially to the Alternaria group, apparently of no clinical significance. In certain instances, at any rate, this lack of clinical significance is more apparent than actual. If one will place some dry weeds on a tripod under a bell jar with an ordinary pollen plate under the tripod, the amount of Alternaria deposit at times will be large. If some of these Alternaria cases in patients with positive skin tests who show no symptoms from atmospheric Alternaria content receive a far larger dosage of Alternaria by more or less prolonged dried weed contact, asthma will be prompt, severe, and prolonged.

I have seen two definite cases of this type, both in children where the original positive Alternaria skin tests had been disregarded and where freedom from symptoms for months had been secured by attention to their more obvious specific etiologies.

In the first child, severe asthma occurred twice from massive dosages of Alternaria, once from building a playhouse out of dried grass and weeds, and once, months later, from cleaning the dried weeds out of an empty lot. In the second child, severe asthma followed hunting a lost baseball in a vacant lot covered with dried weeds. (Neither of these patients clinically or by skin tests was a pollen case.)

I think, then, that we can grant that a certain number of cases that give Alternaria positive skin tests of no apparent clinical significance really are patients definitely clinically sensitive to Alternaria, who will have symptoms from this etiology after a dosage reception more ample than that which they receive from the Alternaria content of the atmosphere.

DR. LEONARD H. HARRIS, Elyria, Ohio.—Dr. Browning has pointed out an incidence of mold reactors of around 25 to 30 per cent but has concluded that his extracts were, for the most part, irritating.

I had hoped that Dr. Feinberg would have analyzed his figures after studying his intracutaneous tests, but since he has not, and since my extracts have more or less followed his methods of preparation, I will show a slide of 130 cases of patients with seasonal hay fever and asthma who were tested with Alternaria intracutaneously. Fifty gave positive reactions. These were not moderate or marked necessarily, but we accepted anything that was positive because we were trying to be impartial. This was an incidence, then, of 38.5 per cent positive Alternaria reactions.

These figures were compared with 130 other cases, of which twenty-six were nonallergic controls, none of whom gave any intracutaneous reactions, and 104 nonseasonal allergic patients, who gave eleven positive reactions to Alternaria.

I asked Dr. Efron to analyze these figures. He compared the fifty positive reactions obtained from 130 seasonal cases, with twenty-six nonallergic controls, all of whom gave negative reactions, and stated that the difference was statistically significant and the extract was therefore nonirritating.

Secondly, he compared the fifty reactions obtained in the 130 seasonal patients with the eleven reactions obtained in the 104 nonseasonal cases and concluded that there was a very significant difference and that, therefore, the reactions were allergic in nature.

By chance I had attempted to do much of what Dr. Feinberg has suggested; namely, to try to decide ahead of time whether one was dealing with a typical mold case or one that was not typical.

Of these fifty patients with seasonal hay fever and asthma that reacted to Alternaria, thirty-four, or 68 per cent, gave a typical mold history, while about 32 per cent gave no such mold history. These were, as I said, intracutaneous tests, and probably not all of them were clinically significant, as far as we could determine. But, certainly, of this group, as I have shown previously, almost all can be given symptoms by blowing powdered Alternaria into their noses.

From this I would conclude that our extracts, by the method of extraction as suggested by Feinberg, are nonirritating, and that the reactions we get in the seasonal cases of hay fever and asthma are clinically significant.

DR. WARREN T. VAUGHAN, Richmond.—There seems to be a difference of opinion. The evidence seems to suggest that the method of preparation of the extract has something to do with the different results.

I wonder whether the discussants would describe what method of preparation they used, as compared to Dr. Browning.

PRESIDENT COHEN.—I think, Dr. Vaughan, Dr. Feinberg, and Dr. Harris are referring to the method that Dr. Feinberg has written about and is in the literature. If I am not mistaken, I think these things are grown in broth and the matt taken off and killed with absolute alcohol, then dried and ground and extracted with some aqueous distillant. Is that not right, Dr. Feinberg?

DR. FEINBERG.—That is essentially correct.

DR. VAUGHAN.—What I was desirous of learning was whether there was a difference in the pH and buffers in the final extracts, whether one would be more permanent than the other.

DR. FEINBERG.—What I say will not be of much help unless Dr. Browning compares his methods with mine.

Our molds are grown, have been most of the years that we have worked with them, in maltose-peptone broth. The pellicles are harvested when they are ripe, of course. Then they are drained of as much fluid as possible and placed in 95 per cent alcohol for purposes of killing the spores and also for dehydrating the material.

They are then allowed to dry thoroughly, ground, then extracted with ether. The ether fraction, of course, is discarded in order to remove lipoids and perhaps some irritating materials. Then the dry powder is again extracted with glycerin-Coca solution, without further buffering. Then the solution is run through a Seitz filter.

DR. BROWNING.—May I ask you to call on Dr. Prince to explain his method.

DR. PRINCE.—I referred to the first type of extract which we were putting up in normal saline with merthiolate to act as a preservative. We used saline because we expected to lyophilize our surplus extracts, and

we thought we could lyophilize normal saline better than we could any of the buffers; naturally, one cannot lyophilize glycerin. But since 1940 all extracts have been made with Hollister-Stier solution, which contains 46 per cent glycerin (by volume) and 4 per cent sodium chloride; there is no buffer in it.

Dr. Milton B. Cohen, Cleveland.—I should like to ask a question. I noticed that the essayists who studied statistically the reactivity of extracts constantly spoke of the diagnostic efficiency of an extract. I presume that they mean the diagnostic efficiency with respect to whether the reaction is immunologically specific. That is quite a different matter than the diagnostic efficiency of the extract, which would have to be, as I see it, determined as Dr. Harris determined it in his cases, by actual exposure to molds out of season and the reproduction of symptoms.

Dr. Browning.—Dr. Prince mentioned a change in his plan of testing. He stated that he is now using 1:100 and 1:1,000 dilutions. He stated that he considered significant a few reactions from the 1:1,000 dilution. One would assume that when he obtains many reactions, he does not consider them significant. In other words, this is just another way of stating that he feels that he is dealing with irritant extracts.

He asked me about my experience with other extracts. I have been running a series with pollens as well as with foods. The pollen extracts apparently are giving a very good diagnostic efficiency. Some of the foods are, but some of the food extracts are definite irritants and, consequently, of no value.

Before taking up Dr. Feinberg's question, I wish to emphasize that this paper refers only to the extracts used in this particular study, and I have no comparison as far as other extracts are concerned. I used only the extracts that were furnished to the members of the Association of Allergists for Mycological Investigation. Certainly our extracts are not very good. Dr. Feinberg pointed out that he can get a clinical history and tell whether his patients are mold-sensitive or not. This is just about as good a plan as using our extracts or perhaps a little better plan.

Dr. Feinberg has divided his patients into two groups. Both groups are definitely selected. In one he has 96 per cent positive reactions and in the other only 3 per cent positive reactions. Apparently he has a very efficient extract from an immunologic standpoint. However, he has not run a control series, and one cannot estimate the efficiency of his extract until this has been done.

Dr. Kahn reported a very definite clinical case. I think all of us see clinical cases that are very definite. I know that I have seen several in which there was no doubt that molds were producing symptoms. However, I would like to point out again that our extracts are not of much value in diagnosing these cases.

Dr. Harris showed some slides and said they had been analyzed by Dr. Efron. I can assure you that they had a very careful analysis if it was done by Efron. However, the slides shown here do not give enough information for analysis and, consequently, one cannot tell whether the extract is an irritant or not.

Dr. Vaughan's question has been answered

Dr. Cohen, we do refer to immunologic specificity.

THE SOURCE OF THE ALLERGIC ACTIVITY OF HOUSE DUST

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FOR a number of years I have been impressed by the frequency with which horse hair and other animal hairs reacted on patients sensitive to house dust. Last year, in making a tabulation for another paper,[1] I found that ninety-five of the one hundred selected patients reacted to house dust and ninety to animal hairs. In that group I thought animal hairs were responsible for producing the symptoms in only 10 per cent. The question arose as to whether that was correct or whether the animal hairs, contacted in other ways than on the live animals, were really responsible for the activity of house dust.

For this inquiry I selected patients from the first one hundred cases in my active file who gave definite reactions to house dust. No patients were used who did not give definite reactions to all house dust extracts tried. The inquiry was further limited to the question of the cause of the skin reaction and less to the question of clinical sensitivity, this in order to keep this paper within the time allotted.

The skin reactions of the one hundred cases to house dust were tabulated alongside of the reactions to the twenty or more common ingredients of house dust. These ingredients are cotton, flax, jute, silk, wool, seven animal hairs, four feathers, kapok, orris root, pyrethrum, glue, and tobacco. Admittedly the list is incomplete. Molds and fungi grow everywhere and can be cultivated from outside air as well as from house dust and house air. Other possible ingredients may be many animal hairs, such as elk, deer, bison and others from trophies; likewise many feathers as pigeon, turkey, parrot and others. Other ingredients may be grass and straw from mats and rugs and also grains and other food materials from kitchens of homes.

The question of a possible pollen content of house dust needs comment. In homes where there are flowers there is the possibility of many flower pollens being present. In my house dust extracts pollen can play no more than an occasional role. The dust samples are collected and the extracts made in the cold winter months since that is the time when most patients with house dust sensitivity are most interested in the house dust problem. I have examined numerous specimens of house dust under the microscope and have yet to find one in which I could demonstrate any pollen granules. Suspending samples in clear mineral oil facilitates the examination.

Read before the Annual Meeting of The American Association for the Study of Allergy, Atlantic City, June 8, 1942.

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The extracts used in this investigation are all concentrated solutions of the extracted materials in Coca's buffered saline solution.[2] The animal hairs are really animal hide as they are made of the full thickness of the animal skin with hair attached, taken from freshly killed animals. The skin is washed in tap water and then chopped into small pieces and first extracted with ether and the ether extract discarded. It is next extracted in Coca's solution for twenty-four hours then filtered through paper, then through Seitz filters and finally bottled in sterile, rubber-capped bottles. All of the extracts are made in the same way.

These saturated solutions are tested first by the scratch method, and the scratch test negatives are then tested by the intradermal method. The animal hairs, cottonseed, flaxseed, and orris root are first tested in dilutions and if negative are then used in the concentrated solution. No test is negative unless negative to the concentrated extract.

None of my extracts are dialized since I have always doubted the wisdom of dialization. The suspension of an extract in a cellophane sack for a week or more at a time allows for oxidation and bacterial action. Even though the resulting extract may contain the same amount of nitrogen as the original, the form of its compounds may be entirely changed by such treatment. There is no proof that such treatment does not result merely in dilution rather than in removal of extraneous material. I believe the reason for so many skin tests being reported as negative in clinically sensitive patients is that most allergists use commercial extracts, all of which are dialized or otherwise diluted until they have little activity remaining. I saw very few such cases.

Many authors have speculated on the content of house dust, but few have offered any definite proof of their ideas. Cazort[3] and Cohen and associates[4] attempted to associate cotton linters with house dust, and Wagner and Rackemann[5] used kapok in a similar study. These studies, in my opinion, were not conclusive.

Many house dust specimens examined under the microscope are composed of mats of hair and cotton fibers with a large proportion of unorganized material. Many specimens appear little different from horse dander. This point is demonstrated in Figs. 1-8. In my experience specimens containing large amounts of hair are most active and those containing no hair are apt to be inert.

The skin reactions of the one hundred cases are shown in Table I. Table II is a summary of Table I. Eight stock house dust extracts were used and thirteen autogenous extracts. Each patient was tested with from one to five of these extracts, and no patient was included who did not react to all house dust extracts tried.

From this study, horse dander is the most common single reactor in patients sensitive to house dust, followed closely by cow and cat hairs. This frequency of sensitivities to horse and cow hairs in an urban, industrial community such as Birmingham was, at first, difficult to under-

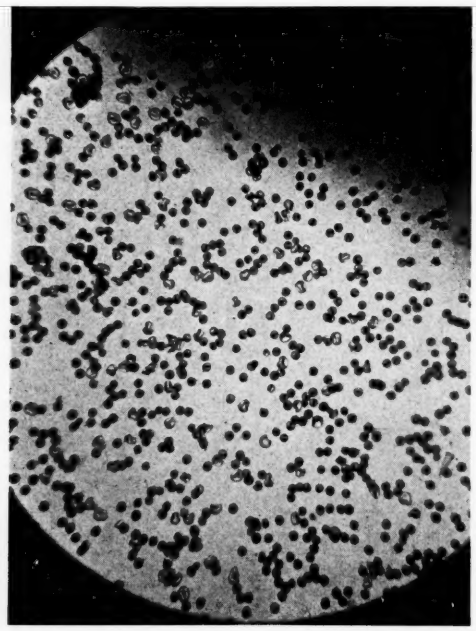

Fig. 1.*—Low ragweed and Bermuda grass pollens (magnification ×600).

Fig. 2.—Cotton fibers (not tested).

Fig. 3.—Sheep wool (few reactions).

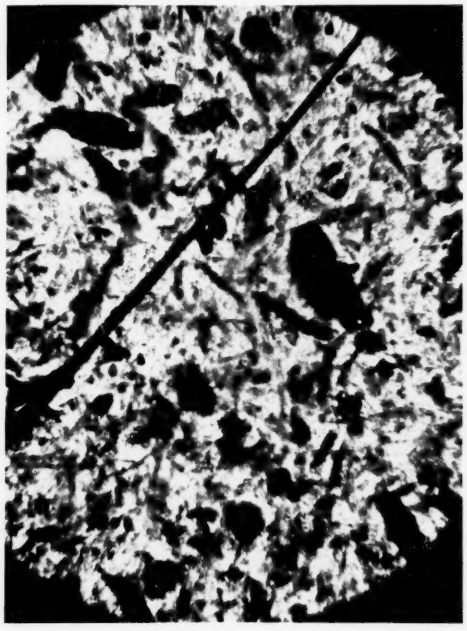

Fig. 4.—Horse dander (many skin reactions).

*Figs. 1-8 are at an approximate magnification of ×100 at the microscope eyepiece and a further magnification of ×6 on the photographic film. Fig. 1 is an artificial photograph of the pollens of low ragweed and Bermuda grass, shown for purpose of comparison, as all photographs are of the same degree of magnification. The materials are all suspended in clear mineral oil and covered with a glass cover slip.

Fig. 5.—Horse dander, hair, and epithelium (many positive reactions).

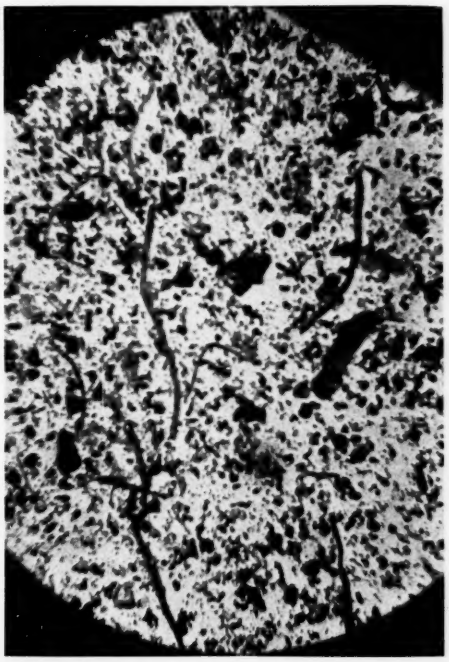

Fig. 6.—House dust (many reactions).

Fig. 7.—House dust—a mat of cotton fibers and hairs (many reactions).

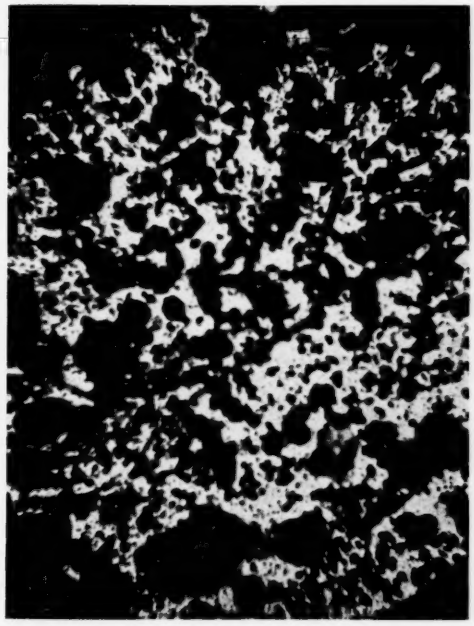

Fig. 8.—School dust (no skin reactions).

TABLE I

RESULTS OF SKIN TESTS ON 100 INDIVIDUALS WITH INGREDIENTS OF HOUSE DUST

NAME	SEX	AGE (YR.)	DATE	DUSTS 3, 4, 5, 6, 8	DUST 10	DUST 11	DUST 12	AUTOG. DUST	COTTONSEED	FLAXSEED	JUTE	SILK	SHEEP WOOL	RABBIT HAIR	HORSEHAIR	HOG HAIR	GOAT HAIR	DOG HAIR	COW HAIR	CAT HAIR	CANARY FEATHER	CHICK FEATHER	DUCK FEATHER	GOOSE FEATHER	KAPOK SEED	OSAGE ROOT	PYRETHRUM	TOBACCO	GLUE
A. A.	F	13	8/40			1		3	0	2		0	0	1	3			1	1	4		0	0		0	0		0	2
G. A.	F	43	10/41				3		0	0		0	0	2	3		1	1	1	1		0	1		0	4	1	0	1
C. A.	M	24	8/41				1		0	4		0	0	1	2			1	2	1		0	1		0	0	0	0	2
R. A.	M	11	4/39	2					1	4		0	0	1	2			1	2	1		0	1		0	1	0	0	2
J. S.	M	29	11/40			4			2	0		0	1	0	3		0	1	1	1		0	1		0	0	1	0	2
R. A.	M	32	11/41				3		0	0	1	0	0	1	3		1	0	1	0		1	0		0	0	1	0	2
R. B.	M	16	11/41				4		0	0		0	0	1	3		3	0	1	0		0	0		0	0	0	0	2
C. A.	M	53	8/40			2			0	0		0	0	0	2		0	1	2	1		0	1		0	0	0	0	2
P. A.	M	29	9/41				2		1	1		0	0	0	2		0	1	2	2		0	1		0	0	0	0	2
E. A.	F	15	11/37	4			3		1	0		0	0	0	1		4	0	0	4		0	1		0	0	0	0	2
J. B.	M	12	12/38	4		4			2	0		0	0	0	3		2	0	1	2		0	1		0	0	0	0	2
C. B.	F	25	9/41				3		1	0		0	0	1	3		1	1	2	1		0	1		0	0	0	0	2
A. B.	F	50	7/41				3		0	1		0	0	0	2		1	1	2	1	0	0	1		0	0	0	0	2
S. B.	F	35	5/41			4			2	3		1	0	0	2		0	1	2	1		0	1		0	0	0	0	2
E. B.	F	25	3/41			2			0	0		0	0	0	1		0	0	1	0		0	1		0	0	0	0	2
B. B.	M	44	7/41						0	0		0	0	1	2		0	1	1	1		0	1		0	0	0	0	2
F. B.	M	10	9/39		4				1	0		0	0	0	3			0	1	1		0	1		0	0	0	0	2
E. B.	M	33	10/41				3		2	2		0	0	1	3		1	0	2	3		0	1		0	0	0	0	2
G. B.	F	30	10/41				3		0	0		0	0	0	2		0	1	2	2		0	1		0	0	0	0	2
P. B.	F	28	9/34	3		3		3	3	0		0	2	1	3		1	0	0	2		3	0	0	0	0	0	0	2
B. B.	F	45	4/40			2			0	1		0	0	0	3		0	0	1	2		0	1		1	0	0	0	2
F. B.	M	13	4/38	3					6	0		0	0	0	3			0	1	2		0	1		0	1	0	1	2
T. B.	M	5	6/39	3					1	2		0	0	0	2			1	2	1		0	1		1	1	0	1	2
A. B.	F	28	6/41			4			1	0		0	0	0	2		1	0	1	4		0	1		0	0	0	1	2
W. B.	M	5	8/40			4			0	0			0	0	1			0	0	0		0	1		0	1	0	1	2
C. B.	F	41	8/39		3	2		3	0	2		0	0	0	2			0	0	1		0	1		0	0	0	0	2

Figures represent degree of response measured as 1+, 2+, 3+, and 4+.

| | | |

TABLE I—CONT'D

NAME	SEX	AGE (YR.)	DATE	DUSTS 3, 4, 5, 6, 8	DUST 10	DUST 11	DUST 12	AUTOG. DUST	COTTONSEED	FLAXSEED	JUTE	SILK	SHEEP WOOL	RABBIT HAIR	HORSEHAIR	HOG HAIR	GOAT HAIR	DOG HAIR	COW HAIR	CAT HAIR	CANARY FEATHER	CHICK FEATHER	DUCK FEATHER	GOOSE FEATHER	KAPOK SEED	ORRIS ROOT	PYRETHRUM	TOBACCO	GILUE
E. H.	M	15	4/41			4			1	0		0	0	3	2		2	0	2	1		0	0		3	2	0	0	3
H. H.	M	49	12/40			2			0	0		0	0	0	1		1	0	1	0		0	0		0	0	0	0	3
W. H.	M	45	10/41				2		0	0		0	1	1	2		0	0	2	0		0	0		0	1	0	0	3
H. H.	M	8	1/39	3					1	0		0	0	0	2		0	0	2	0		0	0		0	0	1	0	3
F. H.	M	12	10/39		3	3		2	0	2		0	0	2	2		0	0	2	0		0	0		0	0	1	0	3
D. H.	M	65	1/41			2			0	0		0	0	0	2		0	1	2	0		0	0		0	0	0	0	3
B. H.	M	20	7/41				3		0	0		0	0	4	2		0	1	2	0		0	0		0	1	1	0	3
M. H.	F	20	1/41			3		3	2	0		0	1	0	3		0	0	3	0		0	0		0	0	0	0	3
W. H.	M	28	9/40			4			2	1		0	0	0	4		0	1	3	1		0	0		0	0	0	0	3
A. J.	M	29	12/40			3			1	3		0	0	0	2		2	0	0	1		0	0		0	0	0	0	3
M. J.	M	45	2/40			3		3	1	2	0	0	0	0	3		1	2	1	2		0	1		0	1	0	0	3
R. J.	M	16	4/40			4			3	3		0	0	0	3		0	1	3	1		0	0		0	0	0	0	3
R. J.	F	29	12/39		2	1		3	0	0		2	0	0	0		0	0	0	4		0	0		0	0	0	0	3
N. J.	F	30	3/40		1	2			2	2		1	0	0	1	0	1	0	3	1		0	0		0	0	0	0	3
S. K.	M	17	3/41			2			0	0		0	0	0	2		0	0	1	1		0	0		0	0	0	0	3
A. K.	F	57	9/40			2			0	0		0	0	0	2	0	0	0	1	0		0	0		0	0	0	0	3
G. L.	F	20	11/41			2	2		2	3		0	0	3	2		2	3	3	3		0	1		0	0	0	0	3
W. L.	M	33	5/40			2			1	0		0	0	0	1		1	0	2	0		0	0		0	0	0	0	3
N. L.	F	25	6/40			2			0	1		0	0	0	1		1	0	2	0		0	0		0	0	0	0	3
S. L.	F	47	10/41			2		2	0	0		0	0	1	1		0	0	1	0		0	1		0	0	0	0	3
L. L.	F	29	10/40			2			2	1		0	0	0	1		0	0	1	0		0	0		0	0	0	0	3
J. L.	F	30	3/41			2			0	0		0	0	0	1		0	1	1	0		0	0		0	0	0	0	3
H. M.	F	32	7/40			2			1	0		0	0	0	2		0	0	2	0		0	0		0	0	0	0	3
E. M.	F	32	8/40			4			0	2		0	0	0	2		0	0	2	1		0	0		0	0	0	0	3
T. M.	M	55	8/39		2				0	0		0	0	0	3		0	0	0	0		0	0		0	0	0	0	3
N. M.	M	11	5/39	4					2	0		0	0	0	3		1	1	1	1		0	1		0	0	0	0	3
J. M.	F	52	8/40			3			0	0		0	0	0	1		1	0	1	1		1	0		3	1	0	0	3
R. M.	F	43	9/40			2		3	0	0		0	0	0	2		0	0	0	0		0	0		3	0	0	0	3
S. M.	M	4	11/38	2					2	2		0	0	0	2		0	1	2	0		0	0		2	0	1	0	3
R. M.	M	5	6/41			3	3	4	0	0		0	0	1	2		0	1	2	0		0	0	0	0	0	0	0	3
W. M.	M	58	1/41			4			1	0		0	0	1	3		0	0	1	1		0	0	0	0	1	0	0	3
D. M.	F	33	7/41				2		0	0		0	0	1	1	0	0	0	1	1		0	0	0	0	0	0	0	3

TABLE II
(SUMMARY OF TABLE I)

TWENTY-ONE COMMON INGREDIENTS OF HOUSE DUST

	DUSTS 3, 4, 5, 6, 8	DUST 10	DUST 11	DUST 12	AUTOG. DUST	COTTONSEED	FLAXSEED	JUTE	SILK	SHEEP WOOL	RABBIT HAIR	HORSEHAIR	HOG HAIR	GOAT HAIR	DOG HAIR	COW HAIR	CAT HAIR	CANARY FEATHER	CHICK FEATHER	DUCK FEATHER	GOOSE FEATHER	KAPOK SEED	ORRIS ROOT	PYRETHRUM	TOBACCO	GLUE
Number tested	128*				13	100	98	4	81	96	86	100	2	58	99	97	99	2	97	85	21	95	97	95	94	89
Reactions						56	37	3	8	10	32	90	0	30	34	71	68	0	12	30	2	34	42	56	36	77
Per cent						56	38	75	10	10	37	90	0	52	34	73	68	0	12	35	10	36	43	59	38	86
Largest reactor	32					8	7	0																		
Reaction equals house dust						8	7		1		5	33			8	14	16					6	6	5	5	25

The twenty-one common ingredients of house dust are listed, showing their comparative reactions in a group of 100 patients sensitive to house dust. Only one patient in the group failed to react to any animal hair. The smallest number of reactions of any individual, not house dust, was 3. The average number not house dust was 7. The largest number was 13. The last line of figures shows the number of patients in whom the reaction to the single ingredient was as large as the house dust reaction and so the one sensitivity alone should explain the house dust reaction.

*Includes all the dusts from 3 through 12.

stand. Few of my patients ever see horses. My first impression was that carpets and rugs might contain much horsehair. I examined carpets through a magnifying glass and they looked like mats of animal hair. I wrote to several nationally known carpet manufactures and all denied the use of any animal hair in their products other than wool. Practically all upholstered furniture, however, contains horsehair, which must be the chief source of contact with this material. Then, too, much of the stuffing in men's coats is horsehair.

The frequency of cow hair sensitivity is likewise difficult to understand. Ozite rug pads used so widely under rugs and carpets are pure cow or hog hair. However, many patients denied having these pads in their homes. It must not be forgotten that every member of a family is constantly walking on floor coverings with cowhide shoe soles. This alone may explain the frequency of cow hair sensitivity.

There is not sufficient time for discussion of all of the allergens listed in the slides. Several others need mention, however. Feathers were among the less common reactors. Duck feather reacted in 35 per cent, chicken in 12 per cent, and goose in 10 per cent; these reactions are decidedly low and is probably contrary to common experience. It may indicate low activity of these test extracts.

The low percentage of reactions to wool is likewise difficult to understand in view of the universal intensive exposure to that allergen. Wool extracts are made from clippings from live sheep and not from sheep hide, as are the other animal hairs, and this may explain the low activity of the wool tests.

There is one other line on the summary slide worthy of special notice, that which shows the largest single reactors. House dust was the largest single reactor in 32 per cent. In the other 68 per cent, one or more other allergens gave reactions as large or larger than house dust, leaving the impression that sensitivity to that one ingredient might explain the whole activity of house dust in that individual.

In 32 per cent horse dander gave reactions as large as those of house dust. In 16 per cent, cat hair and in 14 per cent, cow hair reaction was as large and could have accounted for the whole reactivity of the dust extract. Only one patient failed to react to any animal hairs. All cases in the series reacted to other allergens besides house dust. Three was the smallest number and thirteen the largest, with an average of seven other reactors.

The final proof of the constitution of house dust awaits the development of tests by which to differentiate the almost endless number of allergens. Many authors have presupposed the presence in house dust of some unknown ingredient which would account for its activity. There seems to me to be little reason to look beyond the very self-evident things which occur in our houses and expect to find there some unknown substance.

SUMMARY

House dust is composed of cotton, flax, jute, wool, silk, six or more animal hairs, three or more feathers, glue, kapok, orris root, pyrethrum and tobacco.

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DISCUSSION

ALAN G. COZART.—We agree that the source of house dust antigen is ubiquitous and that it must be something obvious. I should like to refer in more detail to the investigations of Rackemann and Cohen, although you are all familiar with their findings. My own observations, and conclusions from investigation, are not in disagreement with theirs. It has been and is my opinion that the house dust antigen is a specific allergen, resulting from the deterioration of cotton, kapok, and possibly from other cellulose materials.

Efron has drawn certain conclusions from his efforts to produce a highly purified and concentrated antigen, in which he has succeeded to a high degree. Following is his own account:

> We collect house dust as follows: Mattresses, pillows, and upholstered furniture are vacuumed. . . . Most of the furniture and mattresses are stuffed with cotton lint or with kapok. Ninety-nine per cent of the mattresses are filled with cotton lint, so that the principal origins of the house dust are cotton, cottonseed, feathers, and kapok. When we consider the fact that the amount of dust that is obtained from a single mattress is thirty to fifty times that which is obtained from a pillow, and since it is also greater than that which is obtained from upholstered furniture, it follows that the principal origin of the house dust is in cotton, so that if house dust was merely a mixture of its so-called constituents, then we should obtain similar, if not larger, reactions with our cotton extract, or with our fresh cotton lint extract, or with feathers, or with kapok extract. However, such is not the case. We have found no correlation whatsoever between the incidence of specific skin test reactions with purified house dust and with either cotton, fresh cotton lint, cotton seed, kapok, or feathers.

My observations differ from Dr. Davidson's in so many respects that he and I should have to make a lot of definitions to discuss this subject on a common basis. He mentioned 100 selected patients. Unless they were selected on the basis of a typical house dust history, the very high number, 95 per cent, reacting to house dust seems to me to be fantastic. I know wherein the difference lies, I believe. It is in the chief sources of our dust extract and in our interpretation of reactions. Since we know that house dust does contain a variety of substances,

it would be very surprising if it did not cause some slight reaction on every patient sensitive to one or more of its principal constituents. Then there is an added number of reactions differing from the control, due probably to chemical irritants not to be classed as allergens. Consciously or not, we all tend to interpret our reactions in the light of our clinical experience. I think we must do this to avoid many false impressions and conclusions. Dr. Davidson seems deliberately to have excluded influences of clinical experience in reading his reactions. This will, of course, make his figures more scientifically exact, but I fear it will lead to erroneous conclusions.

I think I should call many of his positive reactions negative reactions because experience has shown me that the house dust asthmatic usually reacts by scratch test or by highly diluted extract intracutaneously, with a good wheal with pseudopodia and an itching erythema. On the other hand, the majority of patients who react only weakly to stronger solutions of my extract given intracutaneously cannot be proved clinically sensitive. An extract made from average vacuum cleaner dust is apt to show smaller reactions on patients with house dust histories but many weak or irritative reactions on a group of controls taken at random. It will show many reactions I should consider insignificant. On the other hand, an extract of dust taken from a cleaner which has gone over mattresses and furniture in homes of house dust asthmatic patients will show greater reactions in those clinically sensitive but fewer and smaller reactions in the controls. I think it is a better extract for diagnostic purposes, because it causes reactions more nearly paralleling the clinical sensitivity of the patient.

Dr. Davidson states that in 68 per cent of the patients other allergens gave reactions as great as the house dust. He did not state whether this occurred in comparable dilutions. (From the description of the technique used, one gets the impression that this comparison was not made.)

If the theory that house dust antigen is only a mixture of other antigens is doubted on the skin test basis, it seems untenable to me for clinical reasons. I know too many people with typical house dust histories and with strongly positive skin reactions by direct and passive transfer tests who can sleep with dogs and cats, live with horses, clean chicken houses, use any cosmetics, and handle stock feeds, yet who cannot live in comfort in a clean room which has not had special care to reduce what I call house dust antigen. These people usually are multiple reactors by skin test, but the magnitude of few reactions is comparable to that of my house dust extract. They tolerate pure wool bedding much better than cotton. They can sleep on one cotton mattress and not on another. They leave home and a bare floor, go to a good hotel with pads and rugs on all floors and have the best night in weeks. Better hotels have better quality of cotton in their mattresses and vacuum them often. Even at home they may sleep much more comfortably in one bed than another. The poorer the quality of the cotton in the mattress, and the older it is, usually the less it is tolerated.

Extracts of the bad mattresses cause much greater reactions than extracts of the good ones. These greater or lesser reactions depend on the inherent antigenicity of the extracts rather than on qualitative differences in sensitivity of those tested. The stronger extracts give greater reactions on all house dust cases and the weaker ones give smaller reactions.

I am still playing hide-and-seek with an antigen which has had me mostly on the defensive for forty years. I have seen an extract of feathers from an old pillow react consistently on house dust patients. I could not find evidence of house dust antigen in a jar of fresh duck feathers kept in my office for five years. Five-year-old rayon also failed to cause reaction. Yet cotton linters two years old were active, and it made little difference whether the jars were kept in the dark or light, moldy or not, contaminated with highly active lint from a mattress or not.

It is still my opinion that house dust antigen is a deterioration product of cellulose (cotton and kapok), in spite of certain observations and experiences which I, too, have had which seem flatly to deny this.

DR. DAVIDSON.—I have nothing special to add except to say that the extracts were all concentrated solutions. They were made as concentrated as the Coca solution would take. The final degree of reaction is expressed comparable to that concentrated solution.

My first idea in starting the paper was to try to prove that the activity of house dust solutions depends on the content of animal hair, and I am still very much inclined to believe that that is true, but I could not make it quite definite enough. So I included these other things.

I am certain that the mere fact that two extracts react coincidentally does not necessarily prove that either one of them has anything to do with the reaction of the other. That conclusion has been drawn erroneously in other papers I have seen in the literature recently. I do think that it sheds some light on the subject in some instances, such as this of mine.

PALINDROMIC RHEUMATISM AMONG ALLERGIC PERSONS

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RHEUMATIC persons often suspect that acid foods increase their symptoms and are especially likely to mention tomatoes and strawberries. This is probably based chiefly on hearsay suggestion. Even doctors have been guilty of implanting this idea.

Several years ago a rheumatic patient who believed that tomatoes and strawberries made her worse gave positive skin reactions to these two foods. We found that their ingestion aggravated her symptom. We then did food tests on about twenty-five persons with subacute or chronic rheumatism. Some had other allergic symptoms while others did not. We found no correlation between positive skin reactions and rheumatic flare-ups. Dietary restrictions based upon skin reactions had no effect. Consequently the survey was carried no further. Two considerations have led me to undertake the present study. First, some authors still state that food allergy may be an important factor in the rheumatic state. Pottenger[1] concluded from a study of 150 consecutive patients with arthritis that 94 per cent had gastrointestinal symptoms that were considered due to food allergy. Traut and Vrtiak[2] studied 359 patients with rheumatic heart disease, atrophic or hypertrophic arthritis, and 100 nonrheumatic patients. They concluded that the rheumatic group showed from two to three times as much allergy as the controls.

The second consideration was a small group of allergic persons with intermittent attacks resembling subacute rheumatoid arthritis in whom we have demonstrated specific food excitants. The evolution of the attacks resembled those of intermittent hydrarthrosis, but multiple small joints were involved; often just one hand or foot was affected. Sometimes the reaction occurred in more than one extremity, and at times one or two large joints became inflamed either simultaneously or independently. The local picture was of swelling, redness, pain, and tenderness. The attacks would last from two days to a week, rarely longer. In some, the joints were objectively normal between attacks. In others there were low-grade arthritic changes.

Earlier approaches having been by search for allergy in rheumatic persons, it seemed logical to reverse this, studying arthritis in allergic persons. The present study is of 1,000 consecutive adults with asthma, hay fever, urticaria, angioneurotic edema, migraine, gastrointestinal allergy, or allergic dermatitis (382 males; 618 females). Two hundred and six (20 per cent) complained of rheumatic pains, past or present.

Read before the Ninth Annual Meeting of the American Rheumatism Association, Atlantic City, June 8, 1942.

Except in six instances all received careful physical examination including study of the joints. Of the 200 with rheumatic complaints so studied, ninety showed some evidence of joint pathology. The remainder showed none. Of the ninety with recognizable joint changes, nine were classified as rheumatoid or atrophic and were characterized especially by spindling of the proximal finger joints; 32 were classified as hypertrophic or osteoarthritic, as characterized by nodal enlargement of the terminal finger joints and velvety or sandpaper crepitation of the knee joints; twenty-nine were classified as combined arthritis; and in eighteen involvement was limited to large joints other than the knees. Two cases were traumatic.

Of the 206 with past or present rheumatic complaints, sixty-four were male, 142 female. Of the ninety with joint changes, twenty-five were male, sixty-five female. Sixty-two per cent of all of the allergic patients were women, while 72 per cent of the allergic patients with joint pathology were women.

Of the 206, 143 had allergic symptoms attributable to food: urticaria, angioneurotic edema, gastrointestinal allergy, migraine, atopic dermatitis. However, forty-eight had only inhalant allergy, in which foods appeared to play little or no part, and fifteen had contact dermatitis only. The incidence of food allergy was the same, 69 per cent, in both groups; the 206 with rheumatic history and the 90 with joint changes. Thirty-one per cent of both groups had no important food allergy.

Fifty-five per cent of 749 allergic persons without rheumatic complaint had food allergy. Sixty-nine per cent of 206 allergic persons with rheumatic complaints had food allergy. The 15 per cent higher incidence of food allergy in the rheumatic group may be significant, but aside from this we found no characteristic difference in the allergic pattern between the two groups.

Inferences drawn from the incidence of rheumatism in this series are hazardous. Twenty per cent with history of some form of rheumatism is certainly high. Even 9 per cent with joint changes is high when compared with 0.16 per cent incidence in the Metropolitan Life Insurance Company distribution survey or even with 3.2 per cent in the Massachusetts survey.[3] Our group constitutes a highly selected series of ambulant persons who are sick with another disease and might equally well be compared with the Metropolitan's 9 per cent of rheumatism among all cases of disease, or the Massachusetts' 30 per cent of all persons suffering from chronic disease. Neither survey is statistically comparable with our own.

Of greater interest were twenty-seven patients, 2.7 per cent of the series and 13.1 per cent of those with rheumatic history, who definitely established that certain foods caused rheumatic flare-ups or whose flare-ups accompanied allergic episodes and were relieved with improvement in their allergy, even though they were unable to definitely designate

the causative food. Twenty named the offending foods, while seven found that their rheumatism accompanied allergic episodes and was improved with improvement in the latter. In two members of the second group inhalant allergens appeared to cause rheumatism. One with hay fever, urticaria, recurring pains in the left shoulder, limited motion, and tenderness of this joint at the time of examination, and a negative x-ray thereof, stated that his rheumatism was always worse during the pollen season. The other with asthma, hay fever, and migraine had recurrent pains in the knees and ankles with her asthmatic attacks only. This may have been caused by foods or inhalants, more probably the latter, since the rheumatic symptoms did not accompany her migraine. It is an established fact that inhalant allergens, once absorbed, can cause allergic manifestations elsewhere than in the respiratory tract. Such responses include migraine, urticaria, atopic dermatitis, and angioneurotic edema. In two reported cases anginoid pain occurred only in the pollen season, was relieved with epinephrine, and was prevented by pollen avoidance.[4, 5]

The following foods were mentioned once each as rheumatic offenders: asparagus, barley, cabbage, carrot, cauliflower, celery, chicken, cheese, corn, ham, honey, karaya gum, lamb, peas, peanuts, squash, strawberry, trout, turnip, and wheat. The following were each incriminated by two patients: apple, bean, beef, chocolate, egg, grapefruit, and sweet potato. Orange, peppers, and tomato were mentioned three times; milk, four times; and pork, five times. Except for tomato and strawberry, this list does not include the conventional hearsay foods usually suspected in rheumatism. When tomato or strawberry was mentioned, other foods were also designated. There was another group of six not included in the twenty-seven, because the foods mentioned were members of the hearsay groups and were not subsequently established as offenders. One person incriminated sugars, starches, and greasy foods. Another blamed acid food, strawberry and tomato. A third suspected starches and fruits. The other three blamed sugar, starches, and sweets. The following case illustrates the general group.

CASE 1.—A woman 67 years old had gastrointestinal allergy, recurring angioneurotic edema, and rheumatism in the fingers and right knee. She had moderate spindling of the finger joints, with nodal enlargement of the terminal joints and velvety crepitation of the shoulders and knees. Treatment was limited to allergic dietary restrictions. Eighteen months later she wrote: "Why eat creamed dried beef if my finger joints and knuckles swell so that I cannot clean the dish I cooked the beef in? A thin hamburger is all right once; a big rare juicy one is all wrong. A vegetable salad in a beef gelatin base has caused finger swelling. Corn, asparagus, turnip, sweet potatoes, squash, cauliflower, and cream cheese still cause swelling so that I eat them only at rare intervals. One day we ate out. I had a large serving of barley soup and developed two of the nicest, most painful knees that one could write about. We never have barley, so I looked on my diet sheet and found that it was one of the foods that I shouldn't eat. Along with the stiff knees, I developed a very lame shoulder. The finger swellings lasted about three days. Some of the joints are not normal in size now though they are not too badly deformed."

Among the twenty-seven members of this group the chief complaint was asthma in four, hay fever in seven, urticaria in seven, angioneurotic edema in four, atopic dermatitis in one, contact dermatitis in one, migraine in one, and symptoms of gastrointestinal allergy in two. No patient failed to have a secondary allergic symptom attributable to food allergy, such as urticaria, angioneurotic edema, migraine, or gastrointestinal allergy. Eighteen or two-thirds had urticaria or angioneurotic edema or both.

In the group the usual varieties of joint changes were noted. Four had intermittent hydrarthrosis alone, while a fifth had hydrarthrosis with chronic spindling of the finger joints. All five had hives, angioneurotic edema, or both. Three of the group had what I would term recurrent subacute rheumatoid arthritis, involving the fingers in one case and fingers and larger joints in two. Three had what I would term hypertrophic, or osteoarthritic, as indicated by hypertrophic changes of the terminal finger joints and crepitation on passive motion of the knees. Eight had combined arthritis with spindling of the fingers, terminal nodes, and crepitation of the knee joints. Two of these also had involvement of one or more large joints. One had involvement of large joints alone. In six patients joint examination was entirely negative. Physical examination was not made in two.

I would summarize and interpret the findings in these twenty-seven cases as follows: (1) All had recurrent or chronic joint symptoms, all were allergic, and all had arthritic symptoms attributable to food allergy, although in two cases inhalant allergens were probably responsible for the rheumatic symptoms. (2) Four, approximately 15 per cent, had simple intermittent hydrarthrosis involving large joints. The six with no joint changes at the time of examination may also belong in this group. (3) Thirteen, approximately 50 per cent, showed predilection to involvement of small joints with symptoms resembling rheumatoid arthritis. In some, the joint symptoms were intermittent, in others they were chronic with exacerbations. In the former, one must consider a condition similar to intermittent hydrarthrosis with predilection for small joints, while in the latter one must consider true chronic arthritis with exacerbations caused by allergenic foods. Some of those with negative physical findings may belong in the group with intermittent hydrarthrosis of multiple small joints. (4) Study of this series would suggest that in approximately 2.7 per cent of allergic patients, or 13 per cent of rheumatic patients with clinical allergy, especially allergy to foods, the possibility of an allergic factor as a primary or secondary rheumatic excitant should be recognized. It should be stated parenthetically that there was no case of arthritis deformans in the group of twenty-seven and only one in the entire series of 1,000. Allergic therapeutic measures were unsuccessful in this case.

Solis-Cohen (1914)[6] reported twenty-seven cases fairly closely resembling those in my own series, which he had found in a period of approximately twenty years, to which he gave the term angioneural arthrosis. He emphasized the parallelism of the condition with urticaria, asthma, and angioneurotic edema, also the capriciousness and whimsicality of the phenomenon. He reported seven cases in detail. The first patient came from an allergic family and had pronounced dermographism. The second had dermographism. The third and fourth had drug idiosynerasy. The fifth found that his rheumatic symptoms were provoked by indiscretions in diet. The sixth had dermographism and attacks of sudden burning and itching of the throat of short duration which might have been allergic. The seventh suffered from migraine, urticaria, and paroxysmal dyspnea which may have been asthma.

Kahlmeter (1939)[7] reported fifty-four patients with symptoms generally similar to those in our own patients whom he had observed in a five-year study of approximately 5,000 rheumatic patients. Thirty-five per cent had urticaria, 11 per cent had angioneurotic edema, 13 per cent had asthma, and 9 per cent had migraine. In one-fourth of the cases the joint exacerbations were preceded by gastrointestinal upsets. He believed allergy to be the causative factor in all of the fifty-four.

My series fairly closely resembles the thirty-four patients recently described by Hench and Rosenberg[8] with recurring joint disease without articular residue which they have termed palindromic or recurrent rheumatism. Applying their criteria, our patients probably represent two groups. The ten with negative physical examination or simple recurrent hydrarthrosis comply with their specification of no articular residue. Fourteen, approximately one-half of our series, had joint changes at the time of examination. Our records do not enable us to state whether these changes were permanent or evanescent. Some of them with abnormal joint findings may therefore fall in the palindromic rheumatism class, while others must be considered as chronic arthritis with exacerbations caused by allergenic foods.

Hench and Rosenberg discuss the evidence for and against allergy as an important etiologic factor. They leave this question open, but cite ten points against the allergic theory. There is room for difference of opinion on these points. The absence of familial allergy in 70 per cent of their cases is not conclusive, because anamnesis is often fallacious, minor allergy in other members of the family is often overlooked, the inheritance may skip generations, and allergists are not yet generally agreed concerning the inheritance of the disease. The therapeutic failure of epinephrine, histamine, and histaminase can be paralleled in the more classical allergic diseases. The absence of eosinophilia in the blood or locally is not conclusive. The apparent dissimilarity in the pathologic reactions observed from those of orthodox allergy can be countered by recollection of the large and small joint changes observed

in serum disease. Absence of orthodox allergic skin reactions in 47 per cent, presence of essentially negative skin reactions in 80 per cent, and inability to provoke attacks by giving or to prevent attacks by withholding foods incriminated either by the patient or by skin test reminds us first of the inaccuracy and fallibility of skin reactions to foods and second of the crazy pattern of the allergic response, particularly in that proved allergens may often be eaten at times with impunity. The degree of sensitization to a given food may vary from time to time, and the manner of the clinical response to a single food may change almost overnight, sometimes appearing as migraine, at other times as a gastrointestinal manifestation or urticaria, etc. The following case illustrates these points.

CASE 2.—A 49-year-old man had had intermittent rheumatic pains involving proximal finger joints, the spine, and the right knee over a period of twenty-five years. He averaged about two attacks each year. These lasted from three days to two weeks. There was no limitation of motion of the spine, and x-ray thereof was negative. During acute attacks there was slight swelling, redness and tenderness of the finger joints or moderately pronounced swelling, and pain and limitation of motion in the knee joint with evidence of low-grade regional synovitis with local heat but no redness or tenderness. The only permanent change was velvety crepitation in the right knee joint.

He had two infected wisdom teeth extracted without benefit. He had a chronic bile tract infection which he assumed to be responsible. He had known for years that he was allergic to strawberries, reacting with urticaria at the beginning of each strawberry season. He discovered that if during the season he continued to eat strawberries, he hyposensitized himself so that they ceased causing symptoms. Occasionally strawberries caused diarrhea instead of urticaria.

In May, 1941, at the onset of the berry season, the initial eating caused no urticaria or diarrhea. So he ate more at the following meal. The next morning he had an acute flare-up of his right knee joint which persisted for three days. He had not previously suspected strawberries in connection with his rheumatism. Two weeks later, when his joints were asymptomatic, he again ate strawberries as a trial and within twelve hours his knee was again swollen. On the third day, when the swelling was subsiding, he struck his knee against the corner of a desk, causing recrudescence. Four or five days later with the swelling again subsiding, he went for a three-mile hike, an unusual experience for him. Again the knee flared up. Altogether, this joint reaction, initiated by strawberries, kept going by trauma, lasted two weeks.

He ate no more strawberries and had no rheumatism for a year. In April, 1942, he tried them again. Nothing happened. He then ate them every day for five days. On the third day there was low-grade soreness and swelling of the knee joint, lasting about six hours. On the sixth day he ate raspberries, genetically closely related to strawberries and in our experience sometimes cross-reacting allergically. Three hours later the right knee was swollen, and the next morning the proximal joint of his right thumb was swollen, red, tender. This reaction lasted three days. Skin test to strawberry performed for the first time at the termination of this experiment was negative.

This case illustrates the variability of allergic response symptoms, variability in the intensity of reaction, and the fallibility, at times, of skin tests, although I am not certain that this skin test was altogether

incorrect. The reaction was negative, and the response to ingestion of strawberries in 1942 was slight. Had the skin test been done in 1941 it might have been positive.

The influence of the allergic food reaction on true arthritis is illustrated in the following case.

CASE 3.—A 54-year-old woman with low-grade combined arthritis would have acute flare-ups of the proximal and middle finger joints whenever she ate chocolate. Eggs, to which she also gave positive skin reaction, caused no recognized trouble except as follows: In the spring and summer she works in her garden, planting and digging. When she is eating eggs, the trauma of this work causes subacute flare-ups in her fingers. When she is not eating eggs, the garden work causes little or no discomfort. Here we see a seasonal symptom brought on by a food which is eaten perennially. In one sense, Case 3 is the reverse of Case 2. In Case 2 trauma prolonged a reaction primarily due to strawberries, while in Case 3 eggs exaggerated a reaction primarily due to trauma.

DISCUSSION

The group of twenty-seven patients may be divided into three components. The first had simple intermittent hydrarthrosis involving large joints. The second had similar involvement of small joints, usually more than one, presenting the picture of subacute rheumatoid arthritis. This symptom has not previously been stressed as a part of the picture of intermittent hydrarthrosis. The third component includes persons with rheumatoid arthritis, combined arthritis, and osteoarthritis in whom the ingestion of allergenic foods exaggerates nonallergic arthritic symptoms, the acute exacerbations being "rheumatoid" in appearance.

Approximately one-half of these twenty-seven cases appear to belong in the group which Hench and Rosenberg term palindromic rheumatism. It would appear that food or inhalant allergy may be a cause of palindromic rheumatism. It does not follow that it is the only cause.

We have not followed the 11 per cent of allergic persons with history of rheumatic pains without joint changes to determine whether some of them might fall in the palindromic group.

Skin tests with food extracts are not very reliable. Roughly, about one-half of the offending foods in the group of twenty-seven cases was discovered from skin testing, the other half by the trial and error method, systematized by the keeping of food diaries. Many of our patients were relieved on allergic dietary avoidances. Failure to improve on dietary restrictions based on skin reactions does not rule out the possibility of an allergenic factor. It may be that with improvement in our methods of allergic diagnosis, we will find foods playing a part in more cases. Lewin and Taub[9] reported a proved case of synovitis caused by English walnuts, with positive skin reaction, in which the reaction did not appear until three days after ingestion of walnut. With such a long lag, it might often be difficult to suspect or to establish the cause-and-effect relationship.

Food allergy appears to play no major part in the joint manifestations of the majority of arthritics even though they may be otherwise allergic. However, food allergy played a part of sufficient importance to require its recognition and control in 13 per cent of this series of allergic patients with rheumatic symptoms. When a person with arthritis, especially recurrent arthritis, also has symptoms of food allergy, particularly urticaria, angioneurotic edema, migraine, or unexplained digestive disturbances, allergic food studies should be done. This may apply at times to rheumatic persons without allergic history. A young woman not included in this series had arthritis deformans with no allergic history. Although dietary restrictions based on skin tests did not materially improve her arthritis deformans, the ingestion of pork, ham, or Irish potato always caused exacerbations of the rheumatic symptoms.

Although this series is limited to adults, many of them had rheumatic symptoms in childhood. The frequency with which allergic children complain of intermittent pains in the joints or muscles of the legs, without recognizable joint changes and often with an unexplained blood eosinophilia, has caused me to suspect that allergy, probably food allergy, should be considered as one possible cause for so-called "growing pains." My records do not enable me to state whether this condition should be identified with palindromic rheumatism.

SUMMARY

1. Among 1,000 allergic adults 20 per cent complained of past or present rheumatism. Nine per cent had joint changes, usually low grade. Two and seven-tenths per cent found that certain specified foods produced exacerbation or recurrence of rheumatic symptoms.

2. Some members of this group of twenty-seven had no recognizable joint changes between attacks. They included persons with typical intermittent hydrarthrosis of large joints and others with similar involvement of small joints, the latter usually being multiple.

3. Others in the group had low-grade persistent joint changes, with exacerbations.

4. There are points of similarity between this group and those described by Solis-Cohen, Kahlmeter, and by Hench and Rosenberg. The evidence presented would indicate that food allergy may play a part in recurrent joint exacerbations, especially if the patient presents other evidence of clinical allergy. The condition appears to be fairly infrequent, affecting less than three per hundred adults with allergy. However, it affected thirteen per hundred of a group of persons with rheumatism or history of rheumatism who at the same time had evidence of other clinical allergy.

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Society Proceedings

MINUTES OF THE MEETING OF THE ADVISORY BOARD OF AMERICAN ALLERGISTS, DEC. 4, 1942

After due notice the Advisory Board of American Allergists met at the residence of its Chairman, Dr. Cooke, in New York City, on Friday, Dec. 4, 1942.

Those present were Dr. Robert A. Cooke, Chairman, Dr. Harry L. Alexander, Dr. J. Alexander Clarke, Jr., Dr. Leslie N. Gay, and Dr. Francis M. Rackemann.

Dr. Alexander was present for the first time, representing the American Association for the Study of Allergy, replacing Captain Richard A. Kern, M.C., who is on active duty in the Pacific with the U. S. Navy.

The Committee on Industrial Health of the American Medical Association requested that the report of the Committee on Workmen's Compensation as accepted by this Board be presented in January, 1943, at the Fifth Annual Congress on Industrial Health in Chicago and that the report be published in the transactions of this Congress. This was authorized. It was decided that the report be published in THE JOURNAL OF ALLERGY as well.

The application of one allergy clinic was considered and tabled until such time as adequate clinic records were submitted.

The applications of six candidates for permission to take the examination in allergy were submitted by The American Board of Internal Medicine. Five of these were approved by all the members present. One was disapproved because the applicant's training in allergy was not in accord with the recommendations of this Board as previously adopted and recently published in the November issue of THE JOURNAL OF ALLERGY.

The present status of certification in allergy was reviewed and given considerable discussion.

The situation on certification by The American Board of Internal Medicine to date is as follows:

Sixty-one physicians have been certified in allergy without examination. Five physicians have been certified in allergy by examination.

Certification Without Examination.—All members of both Societies previously certified in internal medicine have been certified in allergy. In December, 1941, eighteen additional men were recommended for certification in internal medicine and in allergy. Six of these were so certified by The American Board of Internal Medicine.

Seven were refused certification in internal medicine without examination. Apparently, the Board did not feel that in 1937, which was their "dead line," these men had fulfilled the requirements for certification in internal medicine.

Four persons failed to fill in properly the application sent to them.

One man had previously failed in the examination for internal medicine and was not considered.

One candidate failed in allergy, having previously passed his internal medicine examination.

Four men were to have been examined in allergy but failed to pass the oral examination in medicine.

It was the consensus of opinion that it was most unfortunate that the American Board of Internal Medicine did not see its way clear to certify the seven men whom they had refused. Some of these men so refused are generally accepted as among our leading allergists. Dr. Cooke, chairman of the Board, was instructed to request the American Board to reopen the discussion.

Generally speaking, the interest in certification has been very healthy, and the younger men seem to be accepting the requirements as published in the November, 1942, issue of the JOURNAL.

J. ALEXANDER CLARKE, JR.
Secretary

Announcement

THE AMERICAN BOARD OF INTERNAL MEDICINE

Pursuant to the policy of the American Board of Internal Medicine to keep fees at a minimum consistent with efficient function of the Board it is now possible to reduce the registration and examination fees. Accordingly, the following action has been directed: The registration and examination fee will be reduced from forty dollars to thirty dollars. The certificate fee will remain at ten dollars, making a total of forty dollars. The oral examination fee in the subspecialties will remain at ten dollars.

This reduction in fees will become effective as of Jan. 1, 1943, and will apply to candidates for the written examination on Feb. 15, 1943, whose applications have not been accepted for a previous examination.

ERNEST E. IRONS, M.D.
Chairman

Selected Abstracts

Dermatology

Under the Direction of Marion B. Sulzberger, M.D., New York, and Joseph Goodman, M.D., Boston

Preliminary Report on the Treatment of Postarsenical Dermatitis With Histamine. Jenkins, E. C.: Ven. Dis. Inform. **24**: 11, 1943.

The author reports the use of histamine (0.1 c.c. to 0.5 c.c. of 1:1,000 histamine dihydrochloride subcutaneously) in patients with exfoliative dermatitis produced by the arsphenamines. Eight patients who were given the usual treatments for postarsenical dermatitis recovered in from ten to fourteen weeks (three cases), showed slight improvement in from fourteen to thirty weeks (three cases), or were not improved in from eighteen to fifty weeks, respectively (two cases). Three other patients who showed no improvement after the usual treatment for nine, twelve, and fifteen weeks showed satisfactory recovery after from three to six weeks of histamine treatment (one injection every other day). Three other patients who were treated with histamine alone (without local treatment of any sort) recovered in from three to four weeks. The author believes that the histamine treatment has produced more satisfactory results than the usual type of therapy for postarsenical exfoliative dermatitis.

Ragweed Dermatitis. Jordon, J. W., Campbell, P. C., and Osborne, E. D.: Arch. Dermat. & Syph. **46**: 721, 1942.

It was found that workers who developed a contact dermatitis as a result of exposure to grain dusts of various sorts frequently showed evidence of sensitivity to ragweed pollen. Nine instances are reported of occupational dermatitis which was not seasonal and which was for the most part accompanied by positive patch tests to grain or related substances and to ragweed extracts as well. The authors point out the importance of polysensitivity in these cases.

Tuberculin Tests in Guinea Pigs With Purified Protein Derivative. Bogen, E.: Proc. Soc. Exper. Biol. & Med. **51**: 221, 1942.

The injection of 0.1 mg. of purified protein derivative (corresponding to 10 or 20 mg. of old tuberculin) into tuberculous guinea pigs resulted only in 2 or 3 plus reactions in the skin, with erythema and edema of varying extent, disappearing in from three to four days without the persisting necrosis or ulceration characteristic of the reaction to 5 mg. of old tuberculin. The systemic or lethal effect of the purified protein

derivative, however, was much greater than that of the old tuberculin. The addition of various substances (such as lampblack) with the purpose of keeping the purified protein derivative longer in situ increased the local effects. In guinea pigs old tuberculin seems to be more sensitive, more specific, less antigenic, and less often lethal as well as less expensive than the purified protein derivative used in these experiments.

Biologic False Positive Reactions for Syphilis Associated With Hyperproteinemia. Cardon, L. C., Atlas, D. H., et al.: Arch. Dermat. & Syph. **46**: 713, 1942.

The authors call attention to the frequency of false positive flocculation tests and anticomplementary complement fixation tests in conditions associated with hyperproteinemia. In thirty-four patients presenting hyperproteinemia associated with various conditions, a false positive flocculation test was found in eight (23 per cent). The authors suggest that blood protein studies should be done whenever a false positive reaction is suspected. They point out also that the false positive flocculation tests are often transient in spite of long-continued hyperproteinemia.

Experimental Cutaneous Reactions of American Blastomycosis in the Guinea Pig. Nelson, L. M.: J. Invest. Dermat. **5**: 257, 1942.

The author demonstrates that guinea pigs injected with *Blastomyces dermatitidis* develop a tuberculin type of sensitivity to the killed organism. Not only do the animals show the tuberculin type of reaction to the killed organism, but also to the broth in which the culture was prepared, a saline extract of the organism, and the polysaccharide derived from the organism. The author believes that the substance which produces the reaction in sensitive animals is in the polysaccharide fraction. He was unable to produce constitutional symptoms in sensitized animals with large amounts of saline extract or polysaccharide solution injected intraperitoneally.

Immunology

UNDER THE DIRECTION OF M. WALZER, M.D., AND
MURRAY ALBERT, M.D., BROOKLYN

Sudden Death Following Injection of Foreign Protein. Vance, B. M., and Strassmann, G.: Arch. Path. **34**: 849, 1942.

Necropsies were performed in seven cases of sudden death following the injection of foreign protein. Two of these patients had had asthma, and five gave no history of asthma. In the nonasthmatic group the deaths occurred from within a few minutes to fourteen hours after the injection of antitoxin containing horse serum and were due to respira-

tory failure. The pathologic findings included marked hyperplasia of the lymphatic tissue, enlargement of the thymus, and marked distension of the lungs. Microscopically, the lungs showed marked distension of the alveoli and a cellular infiltration of the submucous layer of the bronchi in which eosinophiles were present.

One asthmatic patient died in an attack shortly after an injection of a mixture of wool, silkworm, and kapok. The other died in an attack which followed an injection of ragweed extract. In these two patients the pathologic findings were similar to those observed in the nonasthmatic patients. The injection of antitoxin or foreign protein seemed to have caused a spasm of the bronchial muscles so that marked expiratory dyspnea and death by asphyxia resulted. In both the asthmatic and nonasthmatic patients the infiltration of eosinophiles in the submucous layer of the bronchi indicated a long-standing inflammatory reaction which could not have been caused within a few minutes or hours after the injection of foreign protein.

Two theories which might explain sudden death following a foreign protein injection are reviewed. The first theory suggests that the so-called true anaphylactic shock in man is due to acquired sensitivity as a result of a previous injection of foreign protein. The second theory explains the hypersensitivity on the basis of a constitutional factor of a hereditary nature.

In this series and in nineteen cases of sudden death reported in the literature, twelve patients had no history of a previous injection of foreign protein. There was no difference in the nature of the fatal reaction in these cases and in six others who gave a history of having had a previous injection. No difference between the clinical reactions in the asthmatic and in the nonasthmatic patients was noted.

Skin Tests in Schistosomiasis With Antigen From Pneumoneces Mediopleus. Culbertson, J. T., and Rose, H. M.: Am. J. Hyg. **36**: 311, 1942.

The diagnosis of human schistosomiasis by immunologic procedures has been hampered by the difficulty in obtaining suitable antigens. *Pneumoneces plexus*, a fluke commonly found in the lungs of frogs, was studied as a possible antigen. The parasites obtained from the lungs of freshly killed frogs were dried, triturated, and extracted in carbolized saline solution. Patients with schistosomiasis and normal controls were tested intracutaneously with various dilutions of this stock extract. Three patients with schistosomiasis showed immediate positive reactions consisting of a wheal and an erythematous flare while all 12 normal individuals showed negative reactions.

Four patients who had recovered were also tested. Negative skin reactions were obtained in three of them who had been successfully treated from three to six years previously. A slight positive reaction was ob-

served in the fourth patient who had received treatment only two years previously. Hence, an extract made from the lung flukes of frogs contains an antigen which may be satisfactorily employed for specific skin tests in human schistosomiasis.

Cutaneous Reactions to Animal Plasma-Proteins in Man. Savage, G. M., and Taylor, H. L.: J. Immunol. **45**: 261, 1942.

A large series of adult males were tested intracutaneously with the plasma proteins of cow, goat, sheep, horse, hog, rabbit, dog, fox, and man. Detailed studies were made on bovine plasma, because of its suggested use in transfusions. Methods for collecting, fractionating, and preserving bovine plasma and for analyzing it by electrophoresis are described in detail. Intracutaneous tests with 0.05 ml. were done on the forearm. Readings were made at twenty minutes, two hours, and twenty-four hours. The test solutions consisted of extracts of whole animal plasmas, the albumin and globulin fractions of bovine plasma, the products of bacterial metabolism present in the materials, and the preservatives employed. Eight thousand skin tests were performed in 350 individuals. Among those tested with various plasmas, immediate positive reactions were obtained with bovine plasma in 12 per cent of the tests, with goat in 12 per cent, with sheep in 21 per cent, with horse in 21 per cent, with human in 15 per cent, with hog in 18 per cent, with rabbit in 15 per cent, with dog in 34 per cent, and with fox in 40 per cent. The incidence of cross reactions between the different animal species was relatively low. Bovine albumin produced less reactions (2.6 per cent) than whole plasma (12 per cent). Pseudoreactions were frequent and were caused by serum preservatives (azochoramide, merthiolate, sulfanilamide, phenol, etc.) or by the products of bacterial metabolism present in the materials. Although the transfusion of heterologous mammalian plasmas or sera to human beings may produce hypersensitivity to these proteins, it is suggested that this difficulty may be avoided by employing a great variety of animal plasmas or by denaturation of the proteins by alkali. Many of the positive reactions to various plasma proteins reported in the literature are probably pseudoreactions due to various contaminants.

Anaphylaxis in Guinea Pigs Following Sensitization With Chick-Embryo Yellow Fever Vaccine and Normal Chick Embryos. Berge, T. O., and Hargett, M. V.: Pub. Health Rep. **57**: 652, 1942.

Virus and rickettsial vaccines, prepared from infected chick embryo or chick embryonic tissues, are now being employed on a large scale. The question of unfavorable reactions following vaccination with these materials was investigated. Guinea pigs were actively sensitized with vaccines, varying in the age of the embryo employed in their manufacture, and with whole chick embryo extracts. Each animal received

a single sensitizing dose subcutaneously and was shocked after a suitable incubation period with an intracardial injection. An adequate control series was employed. The results obtained in animals sensitized with chick embryo vaccines were similar to those obtained in animals sensitized with normal chick embryo, indicating that the virus or vaccine per se was not responsible for the anaphylactic reaction. It was also found that the anaphylactogenic property of chick embryo was in direct ratio to the age of the embryo and was dependent upon qualitative rather than quantitative factors. Guinea pigs sensitized with chick embryo extract from 10-day-old or younger embryos could not be shocked as readily as animals sensitized with 13- or 14-day-old embryos, even when doses of comparable nitrogen content were employed. Hence, it was concluded that there is a greater likelihood of sensitizing human beings with chick embryo vaccines made from 13- or 14-day-old embryos than with vaccines made from younger embryos.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Experimental and Clinical Observations Regarding the Physiology and Pharmacology of the Nose. Jackson, D. E.: Ann. Otol., Rhin., & Laryng. **51**: 973, 1942.

Jackson presents a very comprehensive report of experimental and clinical observations regarding the physiology and pharmacology of the nose. Kymographic illustrations show the effect of a great variety of drugs on the intranasal air volume, the blood pressure, and the respiration. The drugs used in the experiment consisted of adrenalin, nicotine, sodium nitrite, ether, nembutal, histamine, yohimbine, octin, lobelin, benzedrine, neosynephrine, paredrinol, and propadrine.

Certain Aliphatic Compounds as Nasal Vasoconstrictors. Proetz, A. W.: Arch. Otolaryng. **37**: 15, 1943.

Proetz reports further observations on the use of certain aliphatic compounds as nasal vasoconstrictors. He noted that the immersion of detached specimens of nasal ciliated epithelium of the rabbit in solutions of 2-aminoheptane sulfate and 2-amino-4-methylhexane sulfate for varying periods indicates that these drugs are not deleterious to ciliary activity as applied under clinical conditions. Clinical tests embracing 264 observations indicate that both drugs are effective nasal vasoconstrictors. A 0.5 per cent solution of 2-aminoheptane sulfate approximates in its clinical potency a 2 per cent solution of ephedrine sulfate, and 0.12 per cent solution of 2-amino-4-methylhexane sulfate approximates in its clinical potency 0.5 per cent solution of 2-aminoheptane sulfate. He further states that a 0.2 per cent solution of either drug

introduced into the sinuses by the displacement method is effective and well tolerated. Absorption of these drugs by the nasal mucosa is slow, the effect is prolonged, and a rise in blood pressure does not occur after the nasal application or oral ingestion. No other systemic effect or after-effect has been obtained.

The Allergic Aspect of Vasomotor Rhinitis. Gelfand, H. H.: Arch. Otolaryng. **37**: 1, 1943.

Gelfand presents his observations on the allergic aspect of vasomotor rhinitis with particular reference to etiology, diagnosis, and treatment. He emphasizes the importance of complete clinical history, supplemented by continued clinical observation. He reviews the various occupational contacts which play an important part in the etiology. An analysis is presented of a limited series of fifty-two cases in which twenty-two different substances were incriminated. Most of these were inhalants and a large proportion were met with in the patient's occupation. Food allergy accounted for a small percentage of the cases.

Diagnosis and Treatment of Ménière's Syndrome. Atkinson, M.: Arch. Otolaryng. **37**: 40, 1943.

In the treatment of Ménière's syndrome, Atkinson emphasizes the importance of the accuracy of diagnosis. A neurologic examination should be performed in every case. His observations were confined mostly to the study of cases of sensitivity and nonsensitivity to histamine. Among fourteen patients sensitive to histamine, there was a relief of attacks in twelve. Forty-nine cases of insensitivity to histamine were analyzed. Relief was obtained in twenty patients, improvement occurred in twenty-five; there was a relapse of the condition in four. The patients who were nonsensitive to histamine were treated by the intramuscular injection or oral administration of nicotinic acid. He noted that the histamine-sensitive patients did not respond to nicotinic acid therapy.

Recent Advances in Otolaryngologic Allergy. Hansel, F. K.: Ann. Otol., Rhin., & Laryng. **51**: 1025, 1942.

In a review of the recent advances in otolaryngologic allergy, Hansel abstracts the important points from seventy-three articles selected from a group of about 300. Emphasis was placed upon the recognition of allergy of the parotid and submaxillary glands. This condition is not uncommonly noted in children and may be confused with other types of salivary gland involvement. Papers were reviewed on the following subjects: Allergy of the mouth, the oropharynx, the eosophagus and the larynx, the auditory nerve, allergy and sinusitis in children, allergy in relation to chronic sinusitis, bronchoscopy in asthma, the sinuses in asthma, the pathology and finally the bacteriology of sinusitis.